# Pharmaceutical characterisation of novel microcrystalline cellulose

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*Award date:*
2000

*Awarding institution:*
University of Bath

# Pharmaceutical Characterisation Of Novel Microcrystalline Cellulose

Submitted by
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of the University of Bath
2000







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# Abstract

The effect of relative humidity on flow properties of different powder mixes was investigated at different concentration of colloidal silica. Powder flow was measured using the Aero-flow system which measures the avalanche time. The optimum flow for most of the powder investigated was observed at an optimal relative humidity of 43%. Powder mixes containing Emcocel 90M exhibited improved flow properties compared to powder mixes containing Emcocel 50M. A significant improvement in powder flow was achieved as a result of adding colloidal silica. The best flowability was observed in presence of 2% w/w of colloidal silica. Tablet weight variation was also used as an indirect parameter for assessing powder flow. Results here were similar. The effect of humidity on flow properties was quantified.

The effect of relative humidity on electrostatic charge for different powder mixes was investigated. Electrostatic charge was measured by using the Faraday well system. An increase in the relative humidity from 8% to 93% resulted in a significant decrease in the mean specific charge following flow on a treated plastic chute. However, the increase in the relative humidity has no significant effect in the mean avalanche time profile for silicon dioxide containing grades of microcrystalline cellulose, but was significant for conventional grades. This may be due to the properties of colloidal silica.

Studies of the morphology and distribution of CS in silicified microcrystalline cellulose (SMCC) showed that CS is primarily located on the surface and in the internal regions of some particles of (SMCC).

The influence of mixing time on drug homogeneity and uniformity of low dose drug chlorpheniramine maleate was investigated for binary, ternary and quaternary powder mixes. A satisfactory degree of homogeneity for binary mixes Emcocel 50M/CM, Prosolv 50M/CM and ternary lab mix Emcocel 50M/CM/ colloidal silica (CS) occurred at time mixing of 30, 15 and 5 minutes, respectively. Other excipients like Emcompress and

Lactose required longer mixing time. The effect of mixing on drug homogeneity following addition of magnesium stearate was also studied. Magnesium stearate has caused a dramatic de-stabilising effect on drug homogeneity of most powder mixes investigated. Powder mixes containing Prosolv 50M or 90M were not adversely affected by addition of magnesium stearate.

The effect of mixing time on the electrostatic charges for different powder mixes was investigated. Powder mixes acquired electronegative charges following flow on metal and treated plastic chutes, and electropositive charges using plastic chute. The flow on metal chute was found to be more reproducible between different determination of RSD. Generally, the effect of mixing time on the mean specific charges was not significant.

*Dedication*

*To Mam and Dad*

*To my sons:*

*Suhial, , Yousef and Khalid*

# Acknowledgement

My sincere thanks go to my supervisors Dr Michael Tobyn and Prof. John Staniforth for their enthusiasm and guidance throughout my time at Bath. I have thoroughly enjoyed the work and this is due to Dr Tobyn's friendship approach and his constant encouragement.

I am deeply grateful to my wife for her patience, encouragement and words of wisdom which have comforted me during the difficulties and made my life more happy.

I am indebted to Prof. Kamal El-dene Hussain and Dr. Hashim Ahmed for their words of wisdom, encouragement and help, whenever called upon. Thanks also go to Naser Hasan for all his hard work.

My sincere gratitude to my cousins Hatem, Fisal and Ahmed for their friendship and nice times we spent together.

Financial support from Saudi cultural office is gratefully acknowledged as is the co-operation and help offered by their administrative staff.

I am grateful for the advice and assistance given by a number of the academic staff at Bath, including Dr Stephen Moss. Finally, a special thanks to the past and present members of Glaxo lab and in particular Mo, Martin, Graham, Fraser, Magic, Neha, Rob Pryce Jenny Edge and Margarida. They made being a postgraduate a thoroughly enjoyable occupation.

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# 1. Introduction:

## *1.1. Tablet Excipients: Microcrystalline cellulose and silicified derivative*

In the process of producing various tablets and capsules, the manufacturers are often met by various active substances that exhibit poor flow and inability to be compressed directly in to tablets. Such problems are usually solved by the addition of various excipients such as (gums, sugars, calcium salts etc).

In the 1960's, a new excipient known as microcrystalline cellulose (MCC) was introduced under the trade name Avicel (Edge et al., 1999). This is a semicrystalline polysaccharide produced by partial acid hydrolysis of wood pulp (Landin et al., 1993). It consists of particulate aggregates of cellulose with both amorphous and crystalline regions (Chatrath, 1992). Relative to MCC this material provided effective means for direct compression of tablets and provided a new means for wet granulation processes (Sherwood and Becker, 1998). However, continuous use revealed some drawbacks of this substance related to tablets production. These included:

A) Poor flowability, particularly in case of grades with small particle sizes;

B) Decrease in compaction of tablets following the use of wet granulation processes. There was a decrease in the tablet tensile strength Chatrath, (1992) specially in presence of lubricants e.g. magnesium stearate (Sherwood and Becker, 1998; Vander Watt, 1987).

C) Decrease in bonding capacity following wetting and drying i.e it exhibited what is known as quasi-hornification (Staniforth and Chatrath, 1996).

D) Low bulk density.

E) Sensitivity to moisture since an increase in its moisture content by more than 5% resulted in decrease in its tensile strength and flowability (Amidon et al., 1995). This is attributed to the disruption of hydrogen bond which cross- link the hydroxyl groups in the cellulose chains (Khan et al., 1988).

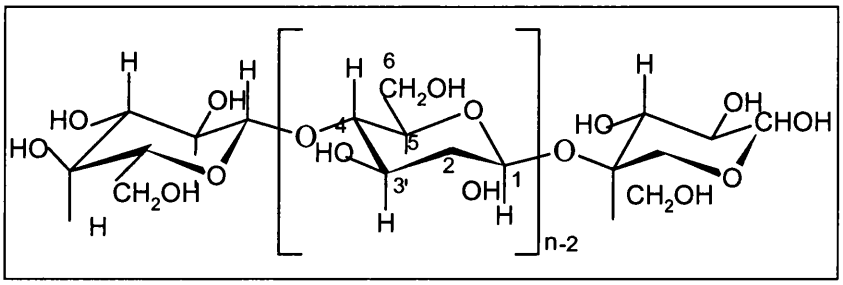



**Figure 1.1:** Microcrystalline cellulose structure (Handbook of Pharmaceutical Excipients, 1986)

Some of these problems were overcome by the introduction of some grades with larger particle size or with high bulk densities but all still suffered from poor compactibility (Staniforth and Tralhao, 1996; Edge et al., 1999; Nicolas et al., 1999).

The demand for an improved MCC resulted in the introduction of a new cellulose product in the mid 1990's that can be used for direct tablet compression or in the wet granulation processes (Tobyn et al., 1996; Hunter et al., 1996).

The new product is a silicified microcrystalline cellulose (SMCC), which is a combination of 2% colloidal silica and 98% MCC.

The silica is usually added after hydrolysis of the wood pulp before spray drying of the product, which was introduced under the trade name Prosolv SMCC.

It is now available in two particle size grades: 50 and 90 μm. The former is recommended for wet granulation processes, while the latter is suggested for direct compression processes (Sherwood and Becker, 1998).

In addition a mixture of the 50 and the 90μm grades can be used for direct compression processes (Sherwood and Becker, 1998).

In this new product no chemical changes were observed in the MCC structure Tobyn et al., (1998), and evidence suggest that, in physicochemical terms, the novel material acts as a simple combination product.

The introduction between $SiO_2$ and the MCC comprised only direct surface physical and within particles contacts (Staniforth et al. 1997b; Edge et al., 1998; 1999).

Studies using water sorption and near infrared spectroscopy revealed that the silicification process did not induce any changes in the physical structure of the MCC except that following wet granulation the SMCC retained its chemical structure whereas MCC failed to do so (Buckton et al., 1999).

Furthermore, physicochemical studies of both MCC and SMCC of the same particle size revealed no significant differences in the true density or crystallinity and both types were free of any cellulose II (Tobyn et al., 1998).

In addition the bulk powders of the 90μm grades of both cellulose showed no difference in pore size distribution. (Tobyn et al., 1998)

However, following wet granulation the SMCC retained its high porosity unlike MCC (Sherwood and Becker, 1998)

Other studies, using scanning electron microscopy and electron probe microanalysis, revealed the presence of $SiO_2$ on the surface and in the internal regions of the SMCC. (Edge et al., 1998)

Furthermore, recent physicochemical and rheological studies performed by Luukkonen et al, (1999) using two types of MCC 50μm. (Avicel 101 and Emcocel 50M) and SMCC (Prosolv50M) confirmed some of the previously known similarities between MCC and SMCC. It also revealed the following findings:

a) There were no significant differences in the particle size of the three celluloses.

b) The specific surface area of SMCC was approximately 5 times that of any of the other two celluloses (6.34$m^2$ per g for SMCC versus 1.014-1.033$m^2$ per g for the others). This has shown before by (Staniforth et al. 1997a)

c) The pore volume size of SMCC was for greater than that of the other two MCC's. This finding is different from that of Tobyn et al., (1998) who reported no difference in the pore volume sizes of MCC 90M and SMCC 90M. This discrepency is probably due to the differences in the methods used. Tobyn et al, (1998) method detects pores grater than 28nm whereas the method utilised by Luukkonen et al, (1999) can detect pores less than 28nm. Indeed, the differences in the pore size observed by the latter researchers were observed in the smaller pores.

d) The flowability of SMCC was for better than that of the other MCCs as reflected by the smaller angle of repose (33.2° in case of SMCC) compared with those of the other cellulose (38.6-39.3°).

e) The bulk and the tapped densities of SMCC were slightly greater than those of the other MCCs as has been observed previously by (Sherwood et al, 1996).

f) SMCC showed smaller swelling volume (4.3ml per g) compared with the other cellulose (4.7ml per g). However, the relative increases on swelling was greater for SMCC. This was because the SMCC (2.86ml per g) powder bulk volume was smaller than the bulk volume of the other MCCs (3.2.ml per g).

There were no differences in the torque development between the three cellulose following mixing of their powders with water.

In field performance studies using SMCC and MCC, experiments revealed the superiority of the strength and hardness of tablets made using MCC (Sherwood and Becker, 1998; Edge et al., 1999). It should be noted that SMCC-induced increase in tablet hardness could have advantages that may include the possibility of reduction in use of excipients and the possibility of increasing the drug concentration for direct compression (reducing the overall tablet size).

It was observed that plain MCC (using the 50μm grade) in wet granulation processes and compaction has the property of losing its porosity by 70% (similar to that reported by Chatrath, (1992)) whereas the SMCC lost only 9% of its porosity i.e. very low densification. These results were a confirmation of those seen by (Sherwood and Becker 1998).

Powder flow studies revealed the improved flowability as reflected by the flow avalanche times of SMCC compared with MCC and indeed tablets made using SMCC

showed very low weight variabilities compared with those made using MCC (Sherwood & Becker, 1998).

In addition, tablets made from SMCC in the presence of the hydrophobic lubricant magnesium stearate in concentration of 0.5% showed greater tolerance to the lubricant-induced decrease in compactibility compared with those made using MCC (Sherwood and Becker, 1998).

In a recent study that dealt with the mechanical properties of compacts made of MCC and SMCC, Edge et al., (2000), found that SMCC produced compacts that possessed very high tensile strength, stiffness, ductility and greater energies for tensile failure compared with those made using plain MCC. Such differences are believed to be due to an interfacial interaction rather than a modification of the bulk MCC properties.

Beside the above benefits the use of SMCC has an additional advantage of a physical mixture of MCC and colloidal silica in that the former use helps in getting reducing to a minimum fumes and dust due to the silicon dioxide. Initial evidence suggests that the physical attachment of colloidal silica is strong enough to stand conventional processing.

Thus, the availability of SMCC may help tablet and capsule manufacturers to enhance the flowability of their powder mixtures with improved uniformity in weights of the produced dosage forms.

It seems that the advantages of SMCC over plain MCC reside in the presence of colloidal silica in the surface regions of the MCC particles.

The presence of some internal silicon dioxide may also lead to an alteration in the interfacial strength that strengthens the product and prevents any interaction with magnesium stearate, which may weaken tablets (Edge et al., 1999).

## *1.2. Flowability of powders*

According to British standards, powders are defined as discrete particles of dry substances with a maximum dimensions <1000μm. The properties of the powders depend upon various factors that include the atomic structure of the chemical constituting the powder (which influences, for instance, the hydrophobicity of the surface), the size, the shape, and texture of its particles, the surface area, density and the electrostatic charges on the surfaces of the particles. Several other factors may also play a part.

These properties collectively determine the rheological properties or the flowability of the powders.

In the manufacture of tablets and capsules the assessment of the flowability of the mixed powders is of great importance. Consistent flowability of the mixed powders during manufacture of the products ensures the consistency and the uniformity of the weights and the strengths (activity) of the dosages together with the consistency in their physicochemical properties when manufacturing different batches of the products. Thus, the availability of different methods to evaluate the flowability of the different powder mixtures is essential in the manufacture of medicines (Neuman, 1967).

Various methods have been developed in terms of the quantitative and the qualitative assessment of the flowability of the different powders. Some of these methods are direct whereas others are indirect.

### 1.2.1. Measurement of the angle of repose

The angle of repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. A simple method to determine this angle is to place a petri dish of known radius (rcm) on a bench surface and to hang over it a glass funnel so that its bottom orifice is 10cm from the bench surface. The outlet of the funnel is filled with the test powder. Then, the bottom of the funnel is opened and the powder is allowed to drop in to the petri dish until the circumference of the petri dish is touched by the pile of the powder. The height (hcm) from the apex of the conical pile to the horizontal surface of the petri dish is measured. The angle of repose can be calculated by:

$$\tan\theta = \frac{h}{r} \qquad \text{Equation 1.1}$$

Generally, angles of repose <25° indicate excellent flowability whereas angles >40° indicate very poor flowability (Wells, 1998).

### 1.2.2. Measurement of Carr's Consolidation Index

In this method 4g of the test powder were placed into a 10-ml cylinder positioned in a tamping apparatus. The initial volume ($V_0$) is then noted. The contents of the cylinder are then tapped 50 times to allow the powder to settle and the new volume ($V_{50}$) is recorded. The following formula is then applied to determine the Carr's consolidation index:

$$\text{Carr consolidation index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100 \qquad \text{Equation 1.2}$$

| Carr's Index | State of Flowability |
|---|---|
| 5 – 15 | Excellent |
| 12 – 16 | Good |
| 18 – 21 | Fair |
| 23 – 35 | Poor |
| 33 – 38 | Very Poor |
| > 40 | Very, Very Poor |

**Table 1.1**. Relation between Carr's index and the powder flowability (Aulton, 1988).

This method is widely used in the characterisation of pharmaceutical powders and several variants exist.

### 1.2.3. The uniaxial compression test

This method is an example of a method that depends upon application of shear force to the sample under test. In this method a hollow split cylinder is filled with the test powder. A force transducer is used to apply a force or a weight from the top of the cylinder onto the powder to consolidate it in a vertical direction for a short known time. The applied consolidation force ($\sigma_1$) is then recorded. Then the hollow split cylinder is removed from around the consolidated powder.

Thereafter increasing vertical load is applied onto the powder until the consolidated powder collapses or cracks. This new weight force ($\sigma_c$) is noted. The smaller this value is the better the flowability of the powder. The value (ffc) usually known as the quotient of consolidation stress and the unconfined yield strength is then calculated by:

The larger this value, the better the flowability of the powder. If the value is > 10, the

$$ffc = \frac{\sigma_1}{\sigma_c} \qquad \text{Equation} \quad 1.3$$

powder is free flowing. If it is between 4-10,the powder is shows adequate flow (Schulze, 1996).

### 1.2.4. The Jenike shear test

This cell consists of a base, a ring that rests on the base, a mold ring, a preconsolidation lid and a shearing lid. The cell is first filled with the test powder using a spoon. The preconsolidation lid is then placed on the powder and a pre-shear stress is applied on it. The sample is then consolidated by applying a number of 90° twists to the lid. A horizontal shearing force is then applied to the ring at a rate of 2 mm per minute until the consolidated powder collapses. ffc can then be calculated as above (Schulze, 1996).

### 1.2.5. Other methods

Other methods available to measure powder flowability include the use of the ramp equipment Kaye, (1997), the triaxial cell, the direct shear cell, the rotational split-level shear cell and the annular shear cell (Kamath et al., 1993 ; Teunou et al., 1999).

## *1.3. The limitations and advantages of some powder flow measurement methods*

Table 1.2. shows the limitations and the advantages of some of the known flowability test methods (Schulze, 1996a;. Schulze, 1996b Kaye, 1995; Kamath et al., 1993).

| Method | Limitations / Advantages |
|---|---|
| Angle of Repose | It indicates the powder flowability under low consolidation stress only. It gives a quantitative statement about the powder flowability so that it can be compared with other powders. |
| Carr's consolidation Index | As above. |
| Uniaxial compression test | The inner wall of the cylinder has to be lubricated to decrease the friction between the powder and the wall.<br>The unconfined yield strength values are small.<br>It is quantitative. |
| Jenike shear tester | The operation of the tester requires good training.<br>It gives quantitative values regarding the flowability of the powder that can be compared with others.<br>It gives a quantitative statement about the effect of time consolidation of the powder.<br>It gives a full idea about the measured shear versus time. |
| Hopper flow rate | It dose not give a quantitative statement a bout the powder flowability and time consolidation.<br>It is simple to operate and very quick. |
| The Ramp Equipment | Can be greatly affected by external vibrations.<br>Not easy to change the environmental conditions in which the powder is avalanching such as humidity and temperature.<br>Not suitable when the powder has a high percentage of fines. These tend to be wafted away from the equipment during the act of feeding the powder onto the ramp.<br>It is a quantitative method.<br>Uses a small quantity of powder. |
| The triaxial cell | The thin latex membrane that contains the powder has to be re-newed for each measurement.<br>During filling of the powder into the membrane a low vacuum is required.<br>The test results are easy to reproduce. |
| The direct shear cell | The flow function cannot be determined from the test.<br>It is quick method to obtain a yield locus. |

**Table 1.2.** Limitations and advantages of some powder flow measurement methods.These limitations have led to the development of novel, alternative methods of powder flow measurement. The Aero-flow is one of these and is described in detail in chapter 3.

## *1.4. Factors that affect the flowability of powder*

Various factors have been noticed to affect the flowability of powders.

### 1.4.1. Particle size

It has been observed that the flowability of most powders increases with an increase in the particle size up to a maximum between 100-400μm. It is dependent upon the type of powder (Onyekweli and Pilpel, 1980). Generally, it is considered that powders with the particle size >200 μm are free flowing whereas most fine powders are subject to cohesion and decrease in the flowability. The flowability of fine powders may have to be enhanced via granulation (Singley and Chaplin, 1982).

### 1.4.2. Particle shape

Particle shape affects powder inter-particle friction, and thus the flow properties of the powder. Powders composed of particles with rounded edges will flow more freely than those with sharper edges or two dimensional flat, flake like particles. Poor flow is often encountered with particles having an interlocking shape or a fibrous Lantz and Schwartz, (1990) quality. It should be noted that microcrystalline cellulose (50μm grade) is a fibrous material (Handbook of Pharmaceutical Excipients, 1986).

### 1.4.3. Moisture content and humidity

An increase in the moisture content of various powders or exposure of the powders to high relative humidities has been consistently observed to decrease the flowability of powders (Teunou et al., 1999).

The increase in the moisture content of the powder due to exposure to high relative humidities allows the trapped water to create liquid bridges between the different particles, facilitates their cohesion and slows flowability. In fact high humidities can lead to caking of various pharmaceutical powders (Kulvanich and Stewart, 1988)

Generally, chemicals differ in their ability to sorb water vapour following exposure to high relative humidities. It has been observed that chemicals with high degrees of amorphous content e.g. starch and polyvinylpyrollidone (PVP) possess high capacities for water vapour sorption (Dawoodbhai and Rhodes, 1989). The water absorbed into the amorphous regions may act as a plasticizer and increase the molecular mobility due to the breakage of the hydrogen bonds between the molecules.

### 1.4.4. Electrostatic charges

Various chemical particles exhibit interparticulate attraction between each other resulting in what is known as cohesive forces. Interactions also occur between particles of different substances giving rise to what is known as adhesive forces (Fuihrer, 1996). The actual interactive forces that operate in powder mixtures include van der Waals, electrostatic and coulombic forces (Staniforth and Rees, 1982c).

*1.4.4.1. Electrification of solids*

Solid surfaces can obtain electric charge in different ways including contact charging and triboelectrification, induction charging, spray charging, corona charging including those of sprayed liquids, ion and electron beam charging, piezoelectric charging, photoelectric charging and charging by mechanical fracture of materials (Hendricks, 1973).

Triboelectrification is electrical charging by rubbing two materials together, which is the oldest known manifestation of electricity record by a Greek philosopher (Thales of Miletus, 600 BC).

Amber was found to become electrified when rubbed with silk and to attract lightweight objects (Cross, 1987). The effect was the result of the accumulation of electric charge on the surface by the phenomenon of triboelectrification. 'Tribo' literally means rubbing (Kaye, 1997), but charge build-up can be achieved by surface contact alone. During contact between two materials, charge moves from one contacted surface to the other. In spite of this long history and the recent development of electronic technology, triboelectricity remains the least understood of electrical phenomena (Peart, 1996). There is no consensus on what charged species are exchanged or on the mechanism by which charging occurs. Nonetheless, tribocharging of powders can be controlled very accurately.

Charge transfer between two different surfaces, when they come into contact, can be explained in terms of electron transfer caused by the difference in work function of the materials.

Electrons exist in the material within various energy levels up to the outermost conduction or Fermi level. The work function ($\Phi$) of a substance is defined as the difference in the energy state between the Fermi level and the vacuum energy level. On

contact between surface A and B, electrons are transferred between the surfaces until the Fermi levels are equalised. The transfer of electrons from one surface to the other causes the generation of a contact potential, which is equal to the difference in work function (ΦA - ΦB).

*1.4.4.2. Triboelectrification in electrophotography*

Electrophotography (xerography) depends upon the ability to control adhesion of electrically charged particles (toner) to charge surfaces (Anderson, 1995). The process consist of six step illustrated in figure 1.2:

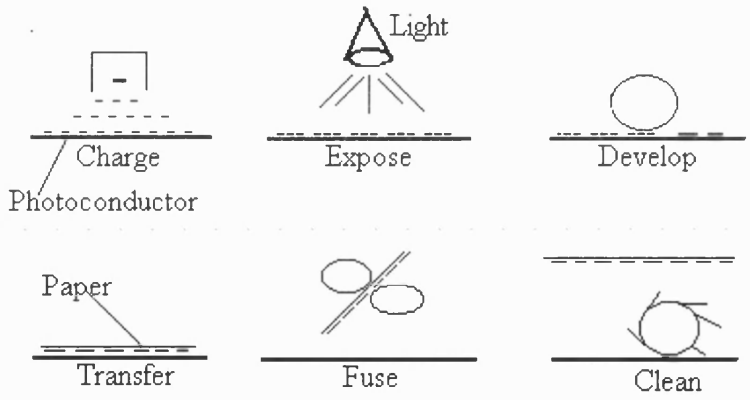



**Figure 1.2**. Schematic demonstration of the electrophotography process showing the six steps in the process.

**Charge:** The photoconductor is charged uniformly using a corona discharge.

**Expose:** The photoconductor is exposed to the image to be produced.

**Develop:** Electrostatically –charged polymer particles (toner) of the appropriate colour are brought into contact with the photoconductor and adhere to it where it is charged.

**Transfer:** The developed image is transferred from the photoconductor to paper or

other surface.

**Fuse:** The image is fixed to the paper by heat and pressure.

**Clean:** Residual toner is removed from the photoconductor and the photoconductor is ready to make the next print.

In electrographic process, the toner particles are brought into contact with photoconductor by mixing them with magnetic particles (carrier). The mixture of toner and carrier is often refereed to as the developer. Electrostatic forces cause the smaller toner particles to adhere to the larger carrier particles. The two-component mixture is transported magnetically to the photoconductor and brushed against it. Toner is removed from the carrier and deposited in the photoconductor under the influence of the electrostatic filed associated with the latent image.

The toner-carrier situation, in xerography, can be considered to be analogous to the drug-carrier interaction in dry powder formulations, such as pharmaceutical blends. Hays, (1994) has shown that electrostatic forces dominate the adhesion of charged toner particles.

*1.4.4.3. Electrical Double Layer*

Derjaguin and Smilga, (1967), have described adhesion electronic theory. In principle, the theory indicates that the formation of an electrical double layer, at the point of contact between two materials, depends on the chemical nature of the substances involved, and their ability to act as either electron donors or acceptors. A donor-acceptor interaction results in positive and negative charges appearing on each surface. Depending on the chemical properties pharmaceutical materials, Derjaguin, (1978), classified some

functional groups in a donor-acceptor series, where each group in the series is an electron acceptor with respect to the preceding group:

donor $-NH_2$ > -OH> -OR> -COOR> $-CH_3$ > -Ph > halogens> C0> -CN acceptor.

The interactive force due to the contact potential, arising from the electron transfer between materials, can be derived as the attractive force on the plates of a parallel plate capacitor (Derjaguin, 1978 and Hendricks, 1973). The electrical force of interaction due to contact can be derived from:

$$F_e = \frac{2\pi q^2}{A} \qquad \text{Equation 1. 4}$$

Where $F_e$ is the interactive force due to contact, q is the particle charge upon detachment, and A is the contact area between the particle and the carrier surface (Stewart, 1986).

Pharmaceutical materials and processing surface, such as metal, develop different contact potentials depending on the chemical nature of the substance and the nature of contact surface. A triboelectric series is considered as organising pharmaceutical materials in a table according to the quantity of charge which is transferred with a particular substrate, e.g. a metal chute. This will enable optimising conditions for specific ordered blend characteristic.

They play an important role in the adhesion process due to development of coulombic and electric double layer interactions. The coulombic interactions usually result from the interactions between uncharged and charged particles in the mixture with the resultant induction of an equal and opposite charge on the uncharged particles figure 1. 3. The electric double layers interactions are due to the formation of a layer of oppositely charged electrons at the interface following contact of particles. (Cross, 1987; Stewart, 1986).

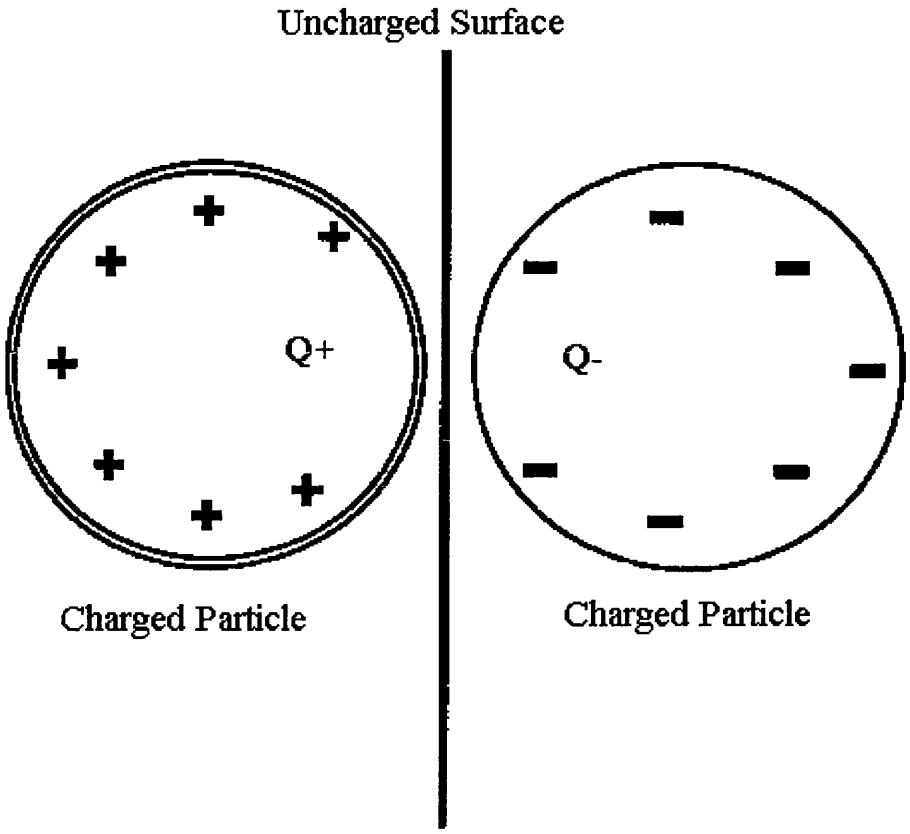



**Fig. 1.3**. Coulombic interactions (Stewart, 1986).

Thus, in mixing two different powdered materials, the two substances may attract each other because of their opposite charges. This may lead to an increase in the bulk density of the powder and hence to a decrease in the flowability. On the other hand, powder mixtures with particles with uniform charges (polarity) will tend to have low bulk densities due to the repulsion forces and hence show good flowability.

Generally, the greater the electrostatic repulsion in the powder mixture, the better is the flowability of the powder (Chem et al., 1979). A practical example of the influence of attractive electrostatic charges in inducing cohesion and poor flowability of a powder was noted a few years ago in plant using terephthalic acid which showed very high bulk density and very poor flowability. However, following the addition of anti-static agent: soyadimethylethyl ammoniumethosulphate (known by the Trade name larostat 264A

manufactured by PPG/Mazer chemicals, USA) in a concentration of 0.05% to the terephthalic acid powder and mixing for 15 minutes there was a significant decrease in the bulk density and clear enhancement in the flowability of the powder (Orband and Geldart, 1995).

The electrical charge generation and decay in various powder particles are shown to be highly affected by the surrounding relative humidity.

In most cases, high relative humidities usually stimulate rapid decrease and disappearance of the electrical charges that accumulated on the particles surfaces. (Boschung and Glor, 1980).

The decrease in charge is believed to be due to an absorption of moisture films on the surface of particles leading to an increase in the electrical conductivity of the surface of the particles and the surrounding atmosphere (Boland and Geldart, 1971).

In most cases an increase in relative humidity is observed to increase the adhesion or cohesion tendency of various particles and to decrease the flowability of their powders (Karra and Fuerstenau, 1977; Stephenson and Thiel, 1980).

Thus in studies concerning powder mixtures it is always advised to measure the electrostatic charges of the involved particles in any mixture.

### 1.4.5. Effect of flow activators or glidants

The flowability of powders can be greatly affected by electrostatic charges, bulk density and humidity. Thus, substance which affect these parameters can greatly modify the flowability of the powders. It has been consistently observed that the flowability of powders can be enhanced by the addition of various substances that can either reduce or alter electrostatic charges. Such substances include talc, maize starch and magnesium stearate. Similarly the addition of substances that coat the powder particles leading to a decrease in moisture absorption together with a decrease in the bulk density (e.g. colloidal silica) also benefit flow. Other substances that have the ability to disrupt the continuous film of adsorbed moisture around powder particles were also found to enhance the powder flowability. Such substances include magnesium oxide, sodium bicarbonate and magnesium carbonate (Sadek et al., 1982).

Addition of various anticaking (or anti-clumping) agents such as tri-calcium phosphate, sodium aluminium silicate and calcium stearate is observed to reduce the bulk densities and to enhance flowability and compaction of some powders (Hollenbach et al., 1982).

#### *1.4.5.1. Colloidal Silicon Dioxide*

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products. It is small particle size and large surface area give it desirable flow characteristics which are exploited to improve the flow properties of dry powder s in a number of processes, e.g., tableting.

Several grades of colloidal silica are commercially available e.g., Aerosil130, 200 300 and 380. The modifications do not affect the silica content, specific gravity, refractive index, colour or amorphous form. However, particle size, surface area and densities are affected. Colloidal silica is hygroscopic, but adsorb large amount of water without liquefying. Some grades of colloidal silica have hydrophobic surface treatments which greatly minimizes its hygroscopicity.

## *1.5. Effect of magnesium stearate*

As this study deals in part with the effect of magnesium stearate on powders flowability a comprehensive note is hereby given about this substance and its influence on powders and tablets.

One of the first uses of magnesium stearate is to act as a lubricant and help to eject the compressed tablet perfectly from the die. It is usually added and mixed with the pre-tablets mixture in a concentration of 0.5-1% (Strickland et al., 1956).

It was originally thought that it acts to form a coat around the individual granules or particles in the mixture but initial scanning electron microscopy failed to detect such layers and hence it was suggested that the chemical acts to reduce asperities and to separate the different mixture particles resulting in a decrease in the interparticulate friction (List and Muller, 1972).

However, later experiments with this substance in tablets mixtures revealed the ability of magnesium stearate to enhance all flow properties such as decreases in the angle of repose and the ratio between tap bulk densities (the so called Hausner ratio) with a resultant increase in flowability of the powder. In these experiments scanning electron microscopy at very high magnification of 15000x revealed the ability of this substance to form a film on a coat round the NaCl mixture particles (Bolhuis et al., 1975).

In addition to the above advantageous properties, magnesium stearate has also been observed to decrease the tablets strength and significantly increased their disintegration time (Ragnarsson et al., 1979).

This effect on the disintegration of the tablets (and many of the other observed effects) is believed to be due to the ability of the chemical to form a hydrophobic film on the surface of the particles leading to the delay in the penetration of water into the tablets (Bolhuis and Lerk, 1982). The prolongation of the disintegration time was found to be proportional to the time of mixing the chemical with the pre-tablet mixture (Ragnarsson et al., 1979). The longer the mixing time, the greater is the disintegration time.

It has also been observed that if in an ordered stable mixture containing salicylic acid and lactose, magnesium stearate is added, loss of the homogeneity of the mixture occurs.

This was initially explained by the ability of magnesium stearate to displace salicylic acid from the lactose and bind to it instead. However, Staniforth and Rees 1982c put the alternative explanation depending upon the differences in the electrostatic charges of the different components. They suggested that since both salicylic acid and lactose are electronegative and magnesium stearate is electropositive, the latter will be strongly attracted to the electronegative lactose resulting in the dislodgement of the salicylic acid from the lactose and hence destabilisation of the ordered mixture. These findings point to the importance of the careful observation of the time of mixing of lubricants such as magnesium stearate with the premixed tablet mixtures (Bolhuis and Lerk, 1981).

Lerk and Bolhuis, 1977, observed that the destabilising effect of magnesium stearate can be reduced by the addition of silicon or talc. The positive effect of colloidal silica was explained by its ability to modify the electrostatic interactions in the quaternary mixture formed (Ahmed, 1989). Similarly, the beneficial effect of talc is attributed to its

electrostatic properties and its ability to fill interparticle void spaces (Staniforth and Rees, 1982c).

In other studies performed by Staniforth and Chadwick (1986) the addition of magnesium stearate was also found to destabilise binary adhesive mixes. The effect of magnesium stearate was reduced by the addition of talc.

## *1.6. Mixing of powders*

Mixing is the process by which particles of two substances or more are brought in contact with each other. The mixing of drug and excipients in tablets and capsules ingredients ensures the content uniformity of the finished dosage form.

Thus, the process of mixing is one of the most important unit operations during production of solid dosage forms. It is at this stage that the likely maximum homogeneity of the solid system is produced prior to final tableting or encapsulation. A number of reviews and literature surveys in the areas of pharmaceutical powder mixing have been produced. Staniforth, 1982, reviewed the process of powder mixing and segregation in relation to pharmaceutical processing. Recent developments in the process of mixing and segregation in different fields of technology after 1976 are presented in a review by Davies (1986).

The unit operation of solid mixing can be separated into four principal stages (Train, 1960).

1. Expansion of the bed of solid particles. This corresponds to the "Principle of Dilatancy" described earlier by Jenkin, (1941).
2. Application of three-dimensional shear force to the powder bed.
3. Mixing for a period sufficient to permit true randomisation of particles.
4. Maintenance of randomisation (no segregation) after mixing has stopped.

### 1.6.1. Theories of Powder Mixing

Several different theories which describe particle associations in powders have been proposed and these include random mixing, non-random mixing, ordered and total mixing.

#### *1.6.1.1. Random Mixing Theory.*

Random mixing is that operation in which motion is transmitted to particles to cause them to assume arrangements such that as mixing proceeds, the frequency of distribution of sample compositions becomes increasingly narrow and approaches the binomial distribution at equilibrium (Weidenbaum and Bonilla, 1955). Random mixing is considered as a statistical process where the bed of particles is continuously rearranged until there is an equal chance of any individual particle being at any given point in the mix at any one time (Yeung, 1979). A random mix may be defined as one where the probability of sampling a particular type of particle is proportional to the number of such particles in the entire mix (Travers, 1988). A truly random mix will contain no cohesive or adhesive forces between different particles (Lacey, 1943) and for this reason random mixes are sometimes referred to as non-interactive (Egermann, 1980) or non-adhesive mixes (Staniforth, 1987). There are three mixing mechanisms which are described for a randomised system.

##### ***1.6.1.1.1. Shear Mixing***

This can be described by the change in the configuration of ingredients through the formation of slip planes in the mixture, where a bulk rearrangement of different sections within the mass takes place. Shear mixing has been described as "three dimensional shuffling", where mixing takes a place across planes of separation (Brothman et al., 1945).

#### *1.6.1.1.2. Diffusive Mixing*

This is described by rearrangement of particles by random movement of particles relative to one another. According to Lacey (1954) diffusive mixing is the distribution of particles over a freshly developed surface. It may occur, for example, in a drum mixer Travers (1988), which is a rotating cylinder in which the powders are lifted past their angle of repose so that the particles tumble over each other.

#### *1.6.1.1.3. Convective mixing*

Described as the movement of groups of adjacent particles from one place to another within the powder mix. Hogg et al. (1966) considered that convective and shear mixing are merely a combination of effects which involve diffusion and breaking up of agglomerates.

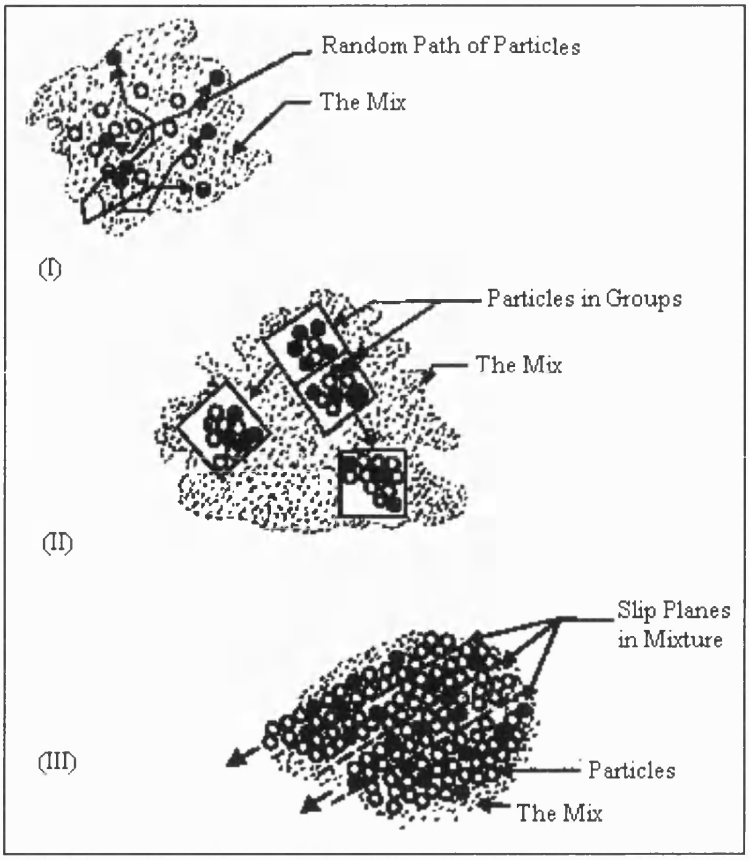



**Fig. 1.4** Main mechanisms of mixing.

(I) Diffusion-random action of individual particles in the mix.

(II) Convection-transfer of adjacent particle groups in the mix.

(III) Shear-configuration change through slip planes.

(After Lantz and Schwartz, 1990).

*1.6.1.2. Non-Random Mixing Theory*

The process of incomplete randomisation by which powder homogeneity can still increase is called non-random mixing (Williams, 1970). The theory of non-random mixing accepts the probability of finding many constituent particles in a mix is not equal.

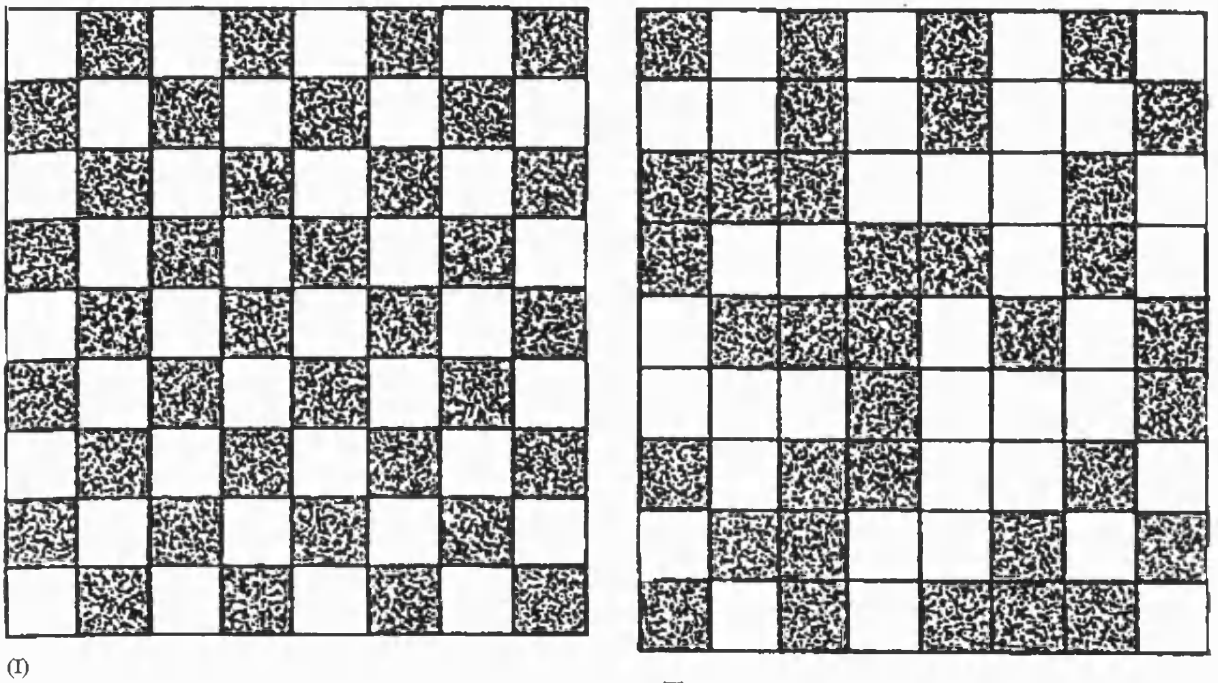



**Figure 1.5**. Comparison between non-random and random binary mixtures.

(I) Non-random mix. (II) Random mix.

*1.6.1.3. Ordered Mixing Theory.*

Due to its direct relevance to pharmaceutical systems, a special emphasis will be given to ordered mixing theory. The adsorption of fine particles onto "host" crystals was first described by Travers and White, 1971 and was found to prevent the segregation normally associated with differences in particle size predicted by random mixing theory. The inaccuracy of applying random mixing theory to describe the particulate associations in pharmaceutical systems was formalised by Hersey in 1975, and an alternative description

was given, i.e. "ordered mixing". Varraes and Kinget, 1980 have stated twofold advantages arising from the formation of ordered mixes:

a) The possibility of better homogeneity than with a random mixture; the homogeneity obtained being dependent on the cohesivity of the drug and the nature of the excipient.

b) The absence of segregation provided that the drug is fully adsorbed and the excipient itself does not segregate.

Hersey and co-workers (Yeung and Hersey, 1979; Yip and Hersey, 1977) observed that mixtures in which drug particles are adsorbed on carrier particles (ordered mixtures) frequently had homogeneities higher than the minimum theoretical variance for an equivalent random mix. In another way such adhesive powder mixes were more ordered than the best random mix and for this reason these workers proposed the term "ordered" for these powder mixes. Such terminology was widely used in literature to describe such particle associations until the late 1970s and early 1980s.

Ordered mixing was described by Hersey in 1977 as the use of mechanical, adhesional or coating forces or methods to prepare ordered units in the mix such that the ordered unit will be the smallest possible sample of the mix and will be nearly identical in its structure to all other ordered units in the mix.

Unlike random mixing, ordered mixing does not proceed to an ideal state by randomisation. For a perfect ordered mix the standard deviation of the distribution of the fine system will be zero, provided the sample size is greater than a single ordered unit. Total variance of such system can be described by the sum of variances due to mixing,

analysis, sampling, purity and other factors. For a near perfect ordered mix where the carrier particles are monosized, the variance will only be a combination of variances due to analysis, sampling and purity. With the assumption that problems associated with the formation of a perfect ordered mix can be overcome, then the measured small variance will be independent of the sample size greater than a one carrier particle diameter. For a random mix the variance is dependent on the sample size withdrawn (Poole et al., 1964). Such a phenomenon was proposed by Yeung and Hersey, 1979 for identifying the formation of an ordered mix. Egermann and Orr, 1983, demonstrated that this method could not be used as a reliable method for determination of ordered mix formation and this has been confirmed in a computer simulation study of mixing by (Lai and Hersey, 1987). They found that an inverse relationship existed between sample standard deviation and square-root of sample size in all mixes except those which contained near monosized carrier particles. This is identical to the situation when a random mix is formed. It was considered that the discrimination of the ordered mix formation from randomisation should be based on other factors including interparticle interactions, degree of homogeneity and segregation tendencies.

#### *1.6.1.4. Total Mixing Theory*

Staniforth, 1982, proposed the concept of total mixing to account for the situation where powder mixes are formed by particles that are not totally randomly distributed nor completely ordered. The theory of total mixing accepts that the two mechanisms, ordering and randomisation exist in a dynamic equilibrium and can be applied to account for the uncertainty at any instant about the type of particle associations in a mix.

Total mixes are established by two main forces:

Gravity and surface electrical forces figure 1.5, (Staniforth 1987a). A real powder mix will owe its final degree of mixedness to both randomisation (stabilised by gravitational forces) and to ordering (stabilised by surface electrical forces), (Johnson, 1975). Such contribution of forces is a function of the characteristics of the constituent particles especially their particle size distribution.

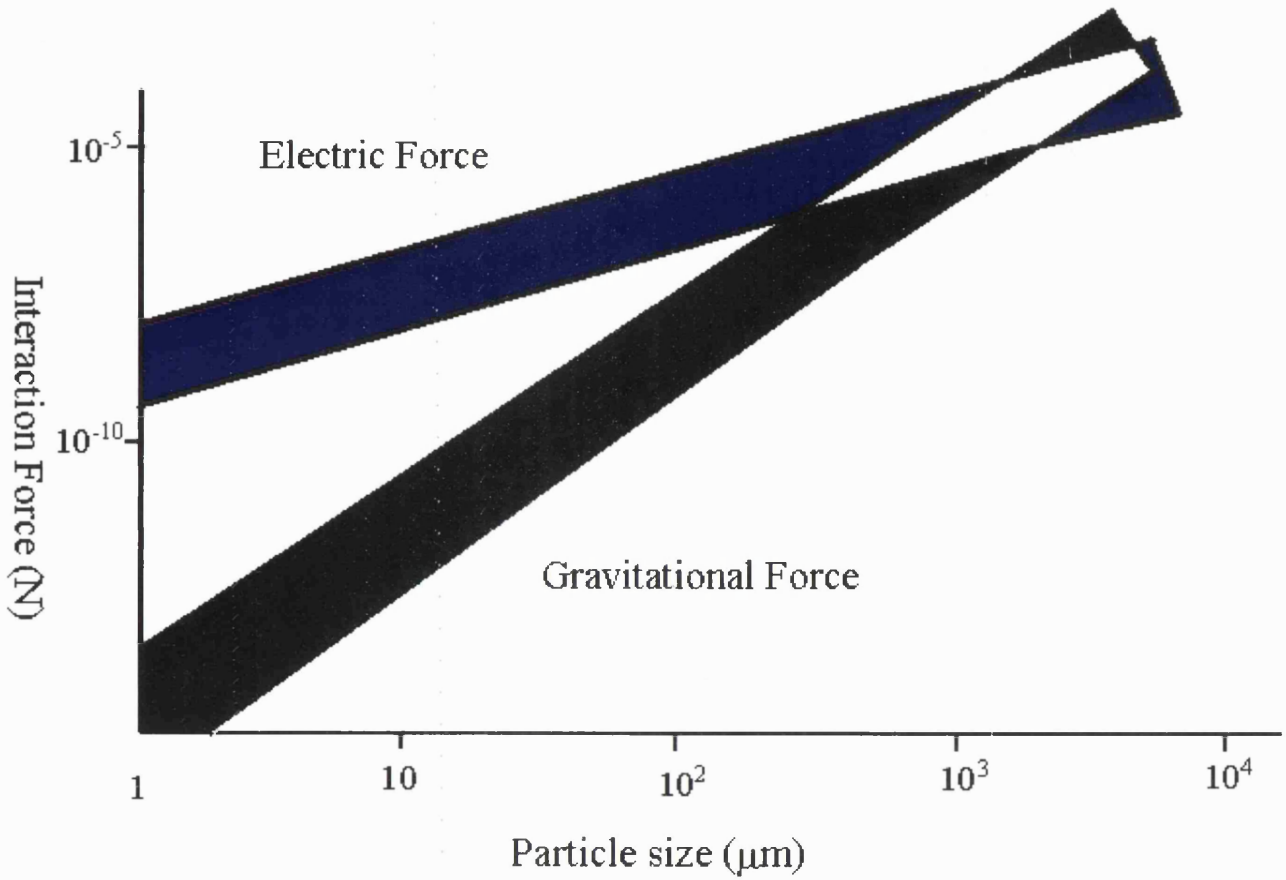



**Figure 1. 6.** Correlation between predominant interaction force and particle diameter (after Staniforth, 1987)

### 1.6.2. Electrostatic powder mixing

The basic idea of electrostatic powder mixing is to give two sets of powders different electrical polarities i.e. negative and positive, and allow the powders to combine under the influence of enhanced electrical forces. The concept of electrostatic mixing is of considerable practical interest since it is expected to produce a uniform stable adhesive mixture (Enstad, 1981a).

Generally, electrostatic mixing of coarse and fine powders in extreme mixing ratios will be feasible provided the following conditions are fulfilled:

1. A satisfactory premix powders exist to the extent that every coarse particle in the powder air suspension is surrounded by a suspension of fine particles.

2. The total electric charge of the carrier is larger than the total charge of the coating material. If this criterion is not fulfilled then the particle will become charged to the same polarity as the coating particles and further coating will be retarded and may even be prevented by electrostatic polarisation.

Electrostatic powder mixing was first attempted by (Tucker and Suh, 1976).

They developed a device that used electrostatic forces to mix two fractions of polyvinyl chloride powder coating resin.

The two fractions were identical in physical properties e.g. size other than colour and were used in equal proportions.

Enstad, 1981b designed and used an electrostatic mixture for blending two different non-pharmaceutical powders of different proportions. The initial experiments which were carried out to demonstrate the process of electrostatic powder mixing were not successful.

The failure was attributed to:

A) lack of sufficient premixing and.

B) Insufficient duration of mixing.

John Staniforth and John Rees (Staniforth, 1980; Staniforth and Rees, 1981 &1982c) investigated the influence of triboelectrification on pharmaceutical powder mixing. Following triboelectrification in an air cyclone constructed of brass, powders were found to have charges at least 100 times greater than those formed after contact with glass surfaces. Optimisation of the triboelectric charging conditions allowed adhesive mixes to be prepared in which maximum electronegative charge was applied to the excipient whereas the drug given a maximum electropositive charge.

Further stability studies showed that adhesive mixes subjected to triboelectrification were less prone to segregation than uncharged powders.

The optimum duration can be found out by withdrawing samples of the mixture at different times during mixing and determining the content of the active substance in the mixture. The mixture homogeneity can be tested by calculating the variance of the concentration of the active substance (Sindel et al, 1998)

### *1.7. Aim Of This Study*

The aim of this study was first to examine the feasibility of utilising an Aero-flow apparatus to reproducibly measure the flow properties of powders, and to develop methods for achieving this. Any correlation between this novel method and conventional techniques would be examined.

The next stage of the study was to discover the properties of silicified microcrystalline cellulose (SMCC, a novel material for use in pharmaceutical processing) in a range of tests relevant to its performance as a tablet or capsule excipient. This material is known to produce stronger compacts in direct compression and wet granulation tablet processes but other factors related to its overall performance were not known.

The flow properties of SMCC compared with more conventional materials, would be characterised using the Aero-Flow and other apparatus. The relative effects of humidity on all these materials was to be quantified and explained, particularly using electrostatic techniques.

Finally the mixing capabilities (in particular the ability to form stable ordered blends), relative to standard materials, would be quantified and explained.

# CHAPTER 2

## *2.0. CHARACTERISATION OF MATERIALS*

Particles can acquire charge when contacted with other substrate surfaces in the absence of an externally applied electric field. When two dissimilar metals are placed in contact a potential difference is produced where electrons will flow more easily from, for example, metal A to metal B than from B to A. Such potential difference is termed contact potential. If metal B is separated from metal A, then metal A will be positively charged and B will be negatively charged (Hendricks, 1973). When the two surfaces, A and B are non-conductors they will be charged in a similar manner, although the charge transfer mechanisms are less well understood.

Measurement of the electrostatic charges can provide useful information regarding the behaviour of particles involved in the formation of adhesive mixes. In general, the larger the difference in magnitude of electropositive and negative charges of two sets of powder particles, the larger will be the likely shared attraction. Potential shared attractiveness can be demonstrated qualitatively using a triboelectric series, which is analogous to an electro-chemical series (Staniforth and Rees, 1982c). Although the triboelectric series is specific to the conditions under which the powders were tested, such a series nevertheless gives a useful indication of the possible interaction between different powders as well as a better understanding of providing mechanisms. The further apart powders with different charge signs are in the series the greater is their likely shared attraction. Potential shared attractiveness can be demonstrated qualitatively using a triboelectric series, which is analogous to an electro-chemical series (Staniforth and Rees, 1982c). Although the triboelectric series is specific to the conditions under which the powders were tested, such a series nevertheless gives a useful indication of the possible interaction between different

powders as well as a better understanding of providing mechanisms. The further apart powders with different charge signs are in the series the greater is their likely shared attraction.

## *2. 1 Materials*

Table 2.1. Details the formulation materials in present study.

| Classification | Material | Batch No, | Supplier |
|---|---|---|---|
| **Carrier** | Microcrystalline Cellulose:<br>Emcocel 50M<br>Emcocel 50M1% SMCC (silicified microcrystalline cellulose) (w/w silicon dioxide)<br>Emcocel 50M 1.7% SMCC<br>Prosolv 50M SMCC<br>Emcocel 90M<br>Emcocel 90M1% SMCC<br>Emcocel 90M 1.7% SMCC<br>Prosolv 90M SMCC | <br>5S5020<br>K5S5001<br><br><br>K5S5002<br>P5B7A03<br>9S5025<br>K9S5003<br>K9S5004<br>P9B7A07 | Penwest Pharmaceuticals Group, Patterson, NY. |
| **Carrier** | Alpha-lactose monohydrate E.P<br>Lactose D30 | 307 | Meggle, Wasserberg, Germany |
| **Carrier** | Dicalcium phosphate<br>Emcompress 200 | N/A | Albright&Wilson company |
| **Drug** | Chlorpheniramine Maleate salt | 12H0396 | Sigma |
| **Lubricant** | Magnesium stearate | N/A | BDH Chemicals Ltd., Poole, U.K. |
| **Glidant** | Colloidal silica<br>(Aerosil 200) | 0891 | Degussa AG, Frankfurt, Germany. |

**Table 2.1.** Details of formulation materials.

### 2.1.1. Abbreviation used in text

| Name | Abbreviation used in text |
|---|---|
| Emcocel 50M or 90M | EM50 or EM90 |
| Magnesium stearate | MS |
| Colloidal silicon dioxide or Colloidal silica | CSD or CS |
| Relative Humidity | RH |
| Mean avalanche time | MAT |
| Mean specific charge | MSC |
| Tablet weight variation | TWV |
| Relative standard deviation | RSD |
| Coefficient of variation | C. V. |
| Chlorpheniramine Maleate | C.M. |
| Lab Mix 50M or Lab Mix 90M | LM50M or LM90M |

**Table 2.1.1.** Abbreviation used in text.

### 2.1.2. Salt Solutions

To study the effect of relative humidity on the powder flow, powders were exposed to various ranges of humidities by sealing the samples in a humidity chamber containing saturated salt solution for a minimum of 48 hours. A constant humidity can be maintained at a given temperature by the presence of a saturated aqueous solution in contact with an excess of solute. Different salt solutions were used to get the required conditions of different relative humidities (Pharmaceutical Handbook, 1988)

1. Potassium Hydroxide Solution (KOH)

An excess amount of KOH (Fisons Scientific Equipment, batch No 9501650 115) was dissolved in distilled water to obtain a saturated solution. This was intended to give at 20C° a relative humidity of 8%.

2. Potassium Acetate ($CH_3COOK$)

An excess amount of $CH_3COOK$ (Fisons Scientific Equipment, batch No 60) was dissolved in distilled water to obtain a saturated solution. This was intended to give at 20C° a relative humidity of 28%.

3. Potassium Carbonate anhydrous ($K_2CO_3$)

An excess amount of $K_2CO_3$ (Fluka Chemie AG CH-9471, batch No 347852/1 796) was dissolved in distilled water to obtain a saturated solution. This was intended to give at 20C° a relative humidity of 43%.

4. Sodium Bromide ($NaBr.2H_2O$)

An excess amount of $NaBr.2H_2O$ (ALDRICH Chemicals Co Ltd, batch No 40414/40408011) was dissolved in distilled water to obtain a saturated solution. This was intended to give at 25C° a relative humidity of 58%.

5. Sodium Chloride (NaCl)

An excess amount of NaCl (ALDRICH Chemicals Co Ltd, batch No 40414/40408011) was dissolved in distilled water to obtain a saturated solution. This was intended to give at 20C° a relative humidity of 72%.

6. Potassium Nitrate ($KNO_3$)

An excess amount of $KNO_3$ (BDH Chemicals Ltd, batch No 29638) was dissolved in distilled water to obtain a saturated solution. This was intended to give at 20C° a relative humidity of 93%.

## *2.2. Methods*

### 2.2.1. Density Measurements:

#### *2.2.1.1 Bulk Density Measurements*

The bulk density is a function of the packing behaviour of powder particles. For any type of packing, failure of the powder bed, for example during flow or mixing is determined by interparticle friction and alters according to the particle size, shape and the material composition. Accurately weighed powder was filled into 100ml (for determining the bulk density of Emcocel) measuring cylinder using a smooth-walled glass funnel. The initial volume, $V_o$, was recorded and the cylinder was placed in a jolting volumeter (Type STAV 2003, J Engelsmann GmbH, Ludwigshafen, F.R.G.), which was operated at approximately 4 Hz. Subsequent volumes, Vn, were recorded after the cylinder had been tapped in increments between 100 and 700 cycles. The consolidated bulk density at equilibrium (De) when consolidation was complete and the initial poured or fluff density (Do) were used to calculate the percentage compressibility of the tested powders according to the equation proposed by (Carr 1965):

$$(De-Do)/De.100 = \text{Percentage compressibility} \qquad \text{Equation 2.1}$$

The Hausner ratio was also determined for each sample using the following relationship (Hausner, 1967)

De/Do Equation 2.2

### 2.2.2. Particle Size Analysis

Particle size analysis of all the materials studied was completed using the technique of laser low angle light scattering (LLALS), with a Malvern Mastersizer X (Malvern Instruments Ltd., Malvern, U.K.). Scattered light from a cloud of droplets traversing the laser beam undergoes a Fourier transform to produce a stationary diffraction pattern upon a multi-element detector. The scattering of the particles is predicted by either Fraunhofer, or more generally Mie theory, and the particle size distribution, by volume, calculated (Malvern training manual, 1993).

For Emcocel samples, 300mm lens was chosen, which allowed detection of particles in the size range 1.2 -600μm. A representative sample of lactose was added directly to the circulating dispersing until an obscuration level of 20-30% was obtained, and the particle size distribution, by volume, calculated.

### 2.2.3. Equilibrium Moisture Content Determinations

The moisture content of powders can affect their compressibility, flow characteristics and can also influence the formation and stability of adhesive mixes as described above in chapter 1. The moisture content of a wet solid may be expressed as mass of moisture associated with unit mass of the moisture-free or 'bone-dry' solid (Travers, 1988). Approximately 1g of each powder as received was accurately weighed using an analytical balance (Type LA 164, Oertling, U.K.) into a wide-mouthed sample boat. Samples were

oven dried at 100C until no further change in powder mass was registered; the final mass was then recorded. During re-weighing care was taken to avoid excessive re-uptake of moisture. The balance was positioned close to the oven and weights were recorded immediately after taking the powder sample from the oven. The determination was repeated on a fresh sample and then the mean of at least three determinations was expressed as the equilibrium moisture content of the powder under ambient conditions.

### 2.2.4. Electrostatic Charge Measurements

Electrostatic measurements were carried out using 0.5g, representively obtained from the spinning riffler, of sample. Each material was tested ten times on the vibrator chute attached from which powders fall in to Faraday well attached to an electrometer (Keithley 610C Electrometer). Each sample was run on three different chutes metal, plastic and treated plastic (plastic chute spread with an anti-static agent). Samples were exposed to a range of humidities by sealing in vessels containing saturated salt solutions for a minimum of 48 hours.

Prior to testing the chute was sprayed with an anti-static spray, to attempt to reduce the variability in electrostatic effects on the plastic chute and called (treated plastic chute).

### 2.2.5. Scanning Electron Microscopy

Particle shape and surface characteristics of powder samples were determined qualitatively using scanning electron microscopy. Patterns of powder were prepared for examination by scattering representative samples of the material to be tested onto adhesive-covered aluminium stub using carbon-coated adhesive fixer. The stubs coated with a thin conducting film of gold which was applied using a sputter coating technique. The sample base was placed under a gold plate electrode at a distance of about 7cm inside

a sputter coater (Type S150B, Edwards Sputter Coater). The sputter coating chamber was then evacuated to a pressure of approx. 1.5 x $10^{-4}$ Bar, and a potential difference of approx. 1.4 kV was applied between the gold-air gap-sample base. Gold ions were deposited over the sample surface over a period of approx. 4-5 min in order to build up sufficient surface coverage. The prepared specimens were examined in a scanning electron microscope using a Jeol 6310 (Jeol instruments Japanese Electron Optics Ltd., JEOL, Tokyo, Japan). Back-scattered electrons were collected and processed by the S.E.M. in order to produce conventional stereographic images of particle surfaces.

### 2.2.6. Surface Area Measurement

Surface area has been measured by using Micromeritics Gemini surface area analyser (One Micromeritics Drive, Norcross, GA 30093-1877).

Total surface area were carried out on accurately weighed sample using a flow – through method having nitrogen as the adsorbing gas and helium as the non adsorbing gas. The samples placed in the apparatus and de-gas for one day then the measurement of the surface area has been taken by using liquid nitrogen in this method.

## *2.3. Results and Discussion*

### 2.3.1. Density Measurement

Poured bulk densities determined for the different excipients classified as diluents were found to lie between 0.33 and 0.39 g $cm^{-3}$. For lubricants/glidants/anti-adhere poured bulk densities were between 0.2 and 0.56 g $cm^{-3}$. The consolidated densities for different diluents studied were between 0.39 and 0.45g $cm^{-3}$ while for lubricants/glidants/anti-adherents the range was between 0.36 and 1.02 g $cm^{-3}$. Emcocel 50M 1.7% was found to have the highest consolidated bulk density of 0.39g $cm^{-3}$.

Depending on the nature of the material, the packing density was found to increase with an increase in the number of jolting cycles, reaching a maximum limiting value corresponding to an equilibrium condition, characteristic of a given material. In general, an increased packing density following consolidation may be considered advantageous in tableting operations for two main reasons. Firstly, die-fill volumes would be correspondingly reduced and secondly an improved flow rate as a result of uniform packing may be produced. The combination of these effects is likely to lead to production of tablets having high weight uniformity. In contrast, lighter powders having lower bulk densities are likely to have a low consolidating strength in hoppers. Although this may reduce strong powder arch or bridge formation, it may also produce a high inertia at rest leading to poor flow uniformity and flooding from hoppers.

Hausner found that the ratio De/Do was a measure of interparticle friction and as such could be used to predict powder flow properties (Hausner, 1967). Hausner showed that powders with low interparticle friction, such as spheres had ratios of approximately 1.2. As Shown in table 2.2 most of the excipient have hausner ratio around 1.2. Yet the lowest Hausner ratio is being for Emcocel WG2, Emcocel WG6 and Emcocel 50M 1.7%. Carr

index values have shown excellent flow for Emcocel WG2, Emcocel WG6, and Emcocel 1.7%. While other excipients show flow properties between good and fair flow. Other surface properties such as shape and roughness may also have an influence on particle packing and therefore on the values obtained in this part of the study.

| Sample | Weight (gm) | Bulk Density (g $cm^{-3}$) Fluff $D_o$ | Consolidated De | Hausner ratio | Carr's index (%) |
|---|---|---|---|---|---|
| Emcocel 50M | 19.41 | 0.33 | 0.40 | 1.20 | 17.50 |
| Emcocel 50M 1% | 21.31 | 0.36 | 0.43 | 1.21 | 16.20 |
| Emcocel 50M 1.7% | 23.25 | 0.39 | 0.44 | 1.14 | 11.36 |
| Prosolv50M | 21.58 | 0.36 | 0.43 | 1.19 | 16.27 |
| Lab mix 50M | 20.49 | 0.34 | 0.44 | 1.29 | 22.27 |
| Emcocel 90M | 21.53 | 0.35 | 0.43 | 1.24 | 18.60 |
| Emcocel 90M 1% | 21.40 | 0.34 | 0.43 | 1.27 | 20.93 |
| Emcocel 90M 1.7% | 22.55 | 0.38 | 0.44 | 1.16 | 13.63 |
| Prosolv90M | 20.50 | 0.34 | 0.39 | 1.15 | 12.82 |
| Lab mix 90M | 22.52 | 0.37 | 0.45 | 1.20 | 16.66 |
| Emcocel WG6 | 21.16 | 0.36 | 0.40 | 1.12 | 10.00 |
| Emcocel WG2 | 23.48 | 0.39 | 0.42 | 1.08 | 7.14 |
| Magnesium stearate | 21.37 | 0.23 | 0.36 | 1.54 | 36.11 |
| Colloidal silica | - | 0.03 | 0.05 | 1.56 | 36.00 |

**Table 2.2.** Bulk densities, Hausner ratio and compressibility values for different powder samples.

### 2.3.2. Particle Size Analysis

| Material | D(0.1) µm (n=10) | | D(0.5) µm (n=10) | | D(0.9) µm (n=10) | |
|---|---|---|---|---|---|---|
| | Mean | S.D | Mean | S.D | Mean | S.D |
| Emcocel 50M | 19.922 | 1.11 | 63.26 | 4.06 | 156.79 | 6.39 |
| Emcocel 90M | 25.169 | 5.61 | 110.1 | 3.25 | 220.04 | 16.92 |
| Chlorpheniramine | 23.082 | 1.70 | 91.12 | 5.49 | 246.16 | 3.42 |

**Table2.3.** Particle size of different powder samples.

Particle size analysis of Emcocel 50M, 90M and chlorpheniramine maleate were determined as described in section 2.2.2. and the data are summarized in table 2.3. The mean particle diameters for Emcocel 50M, 90M and chlorpheniramine were found to be 63.26, 110.1 and 91.12 respectively.

### 2.3.3. Surface Area Measurements

A summary of the data for the specific surface areas determined using Micromeritics Gemini surface area analyser for different powders is given in Table 2.4.

| Sample Name | Specific Surface Area ($m^2$ $g^{-1}$) |
|---|---|
| Emcocel 50M | 1.10 |
| Prosolv 50M | 5.76 |
| Lab Mix 50M | 3.05 |
| Emcocel 90M | 1.23 |
| Prosolv 90M | 5.51 |
| Lab Mix 90M | 3.29 |
| Chlorpheniramine Maleate | 0.15 |
| Colloidal Silica | 183 |
| Magnesium Stearate | 14.39 |

**Table2.4.** Specific surface areas of different powder samples.

Colloidal silica was found to have an extremely larger surface area corresponding to 183$m^2$ $g^{-1}$. Magnesium stearate found to have a specific surface area of approximately 14.39$m^2$ $g^{-1}$. Prosolv50M and 90M showed higher specific surface area compared to the other Emcocel excipient. This would indicate that there is a different distribution of the silica in the samples. In dry mix samples it would appeared that the distribution of silica is not optimum as seen by the scanning electron microscopy and discussed in section 3.4.6.

### 2.3.4. Equilibrium Moisture Content Determinations

Equilibrium moisture contents for different powders are shown in Table 2.5.

| | Relative Humidity | | |
|---|---|---|---|
| Sample Name | 8% | 58% | 93% |
| Emcocel 50M | 3.10 | 5.00 | 6.49 |
| Emcocel 50M 1% | 3.09 | 4.80 | 6.30 |
| Emcocel 50M 1.7% | 4.79 | 5.10 | 7.09 |
| Prosolv50M | 4.39 | 5.10 | 6.85 |
| Lab mix 50M | 4.09 | 5.20 | 7.60 |
| Emcocel 90M | 3.58 | 4.90 | 8.10 |
| Emcocel 90M 1% | 4.79 | 4.40 | 6.70 |
| Emcocel 90M 1.7% | 4.89 | 4.81 | 7.10 |
| Prosolv90M | 4.58 | 4.62 | 6.80 |
| Lab mix 90M | 4.40 | 5.20 | 6.70 |

**Table 2.5.** Equilibrium moisture contents for different powders at different relative humidity.

### 2.3.5. Scanning Electron Microscopy

Figures (2.1 - 2.6) show representative scanning electron photomicrographs of particles and particle surface details corresponding to each of the materials used during the present study. The functional significance of specific morphologies will be referred to in relevant sections of discussion in 3.4.6.

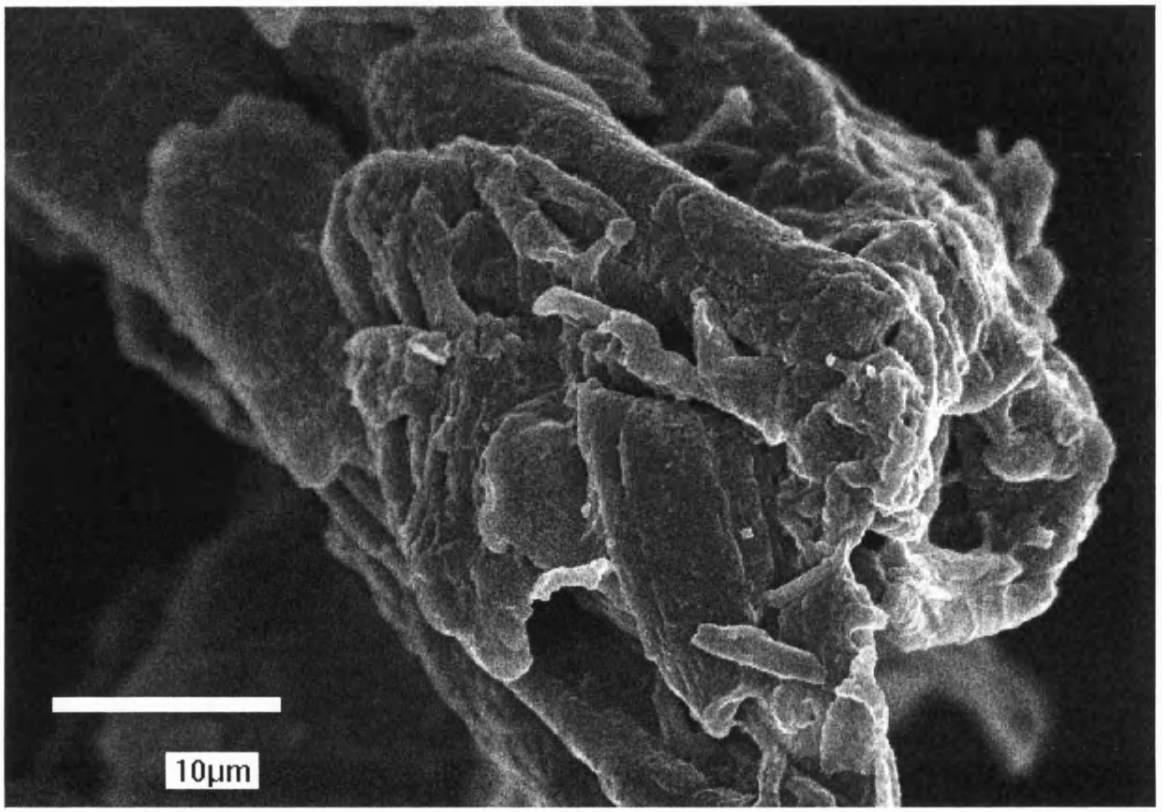



**Figure 2.1.** Scanning electron microscopy of Emcocel 50M.

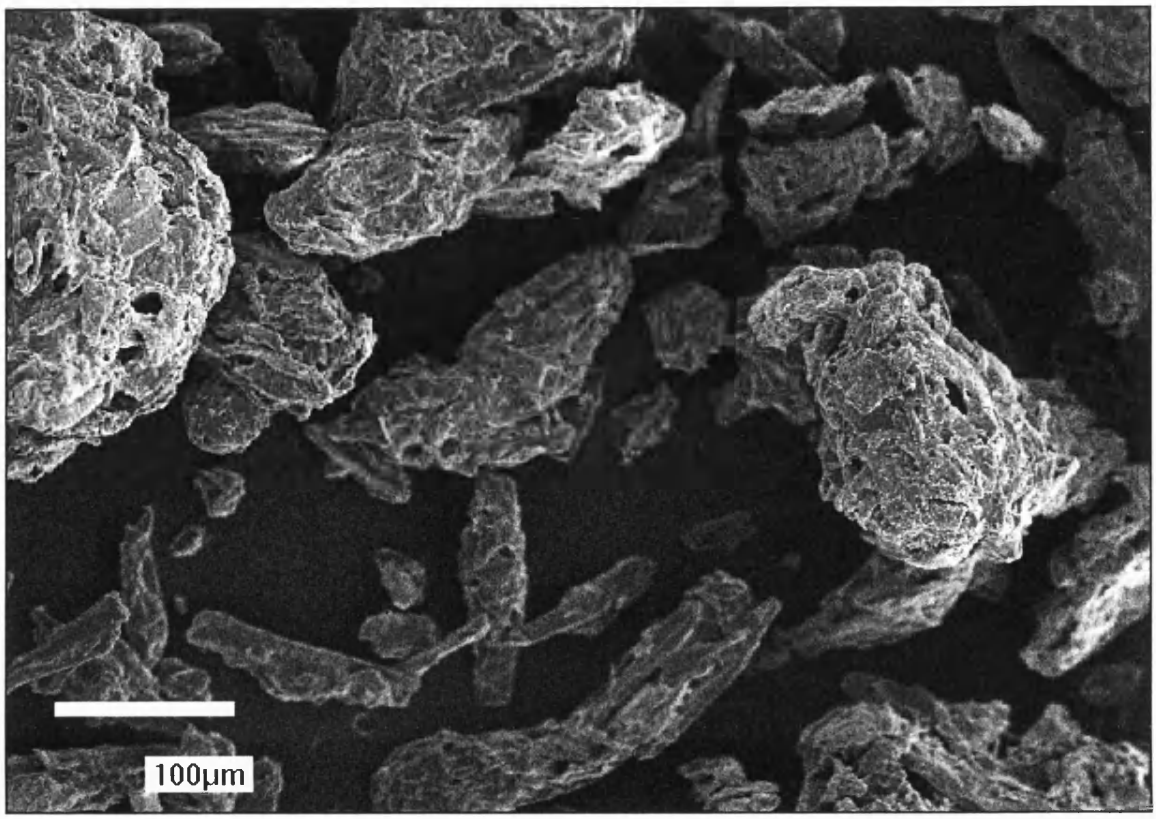



**Figure 2.2.** Scanning electron microscopy of Emcocel 90M.

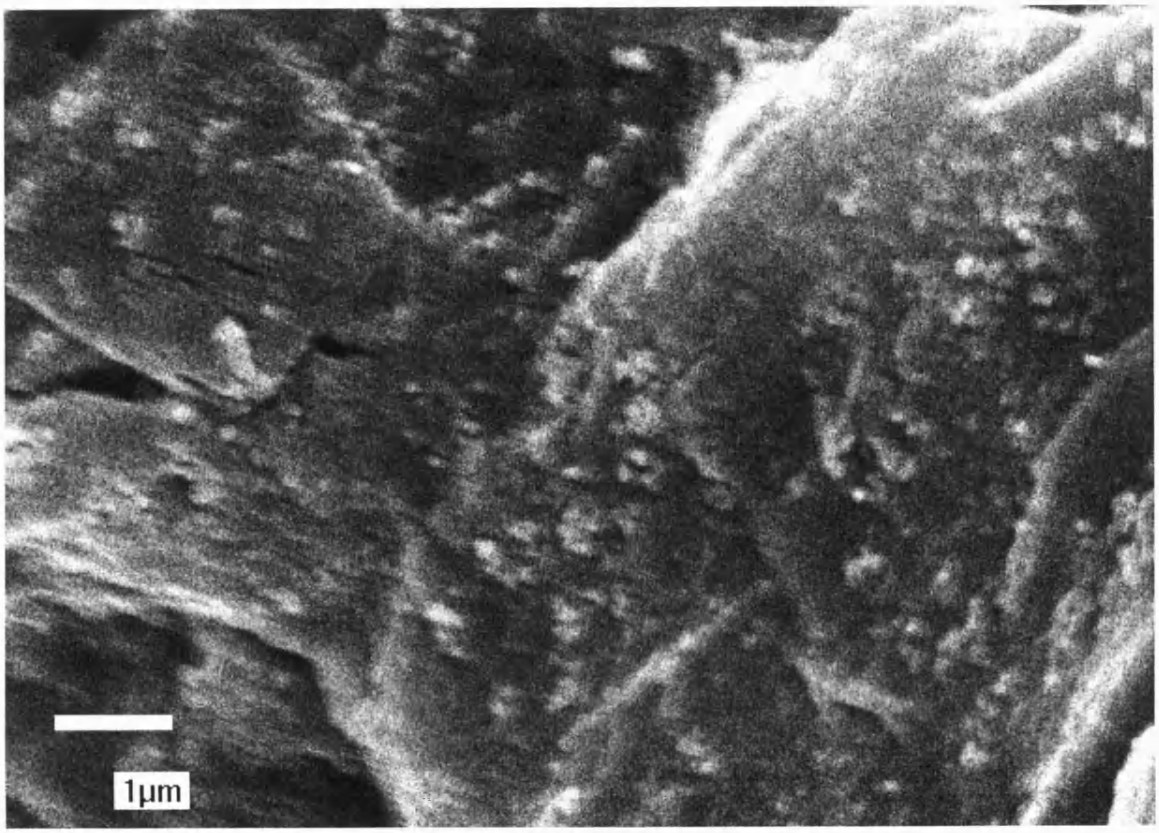



**Figure 2.3**. Scanning electron microscopy of Prosolv50M

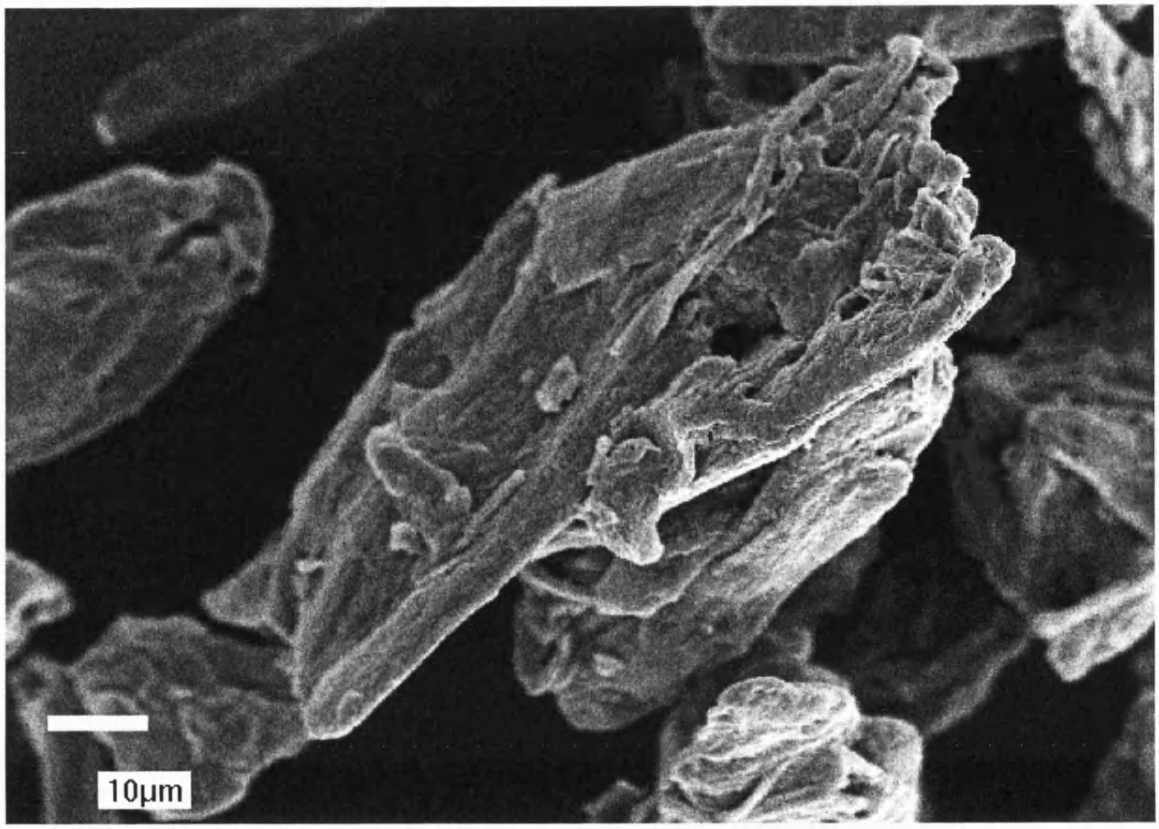



**Figure 2.4**. Scanning electron microscopy of Prosolv50M.

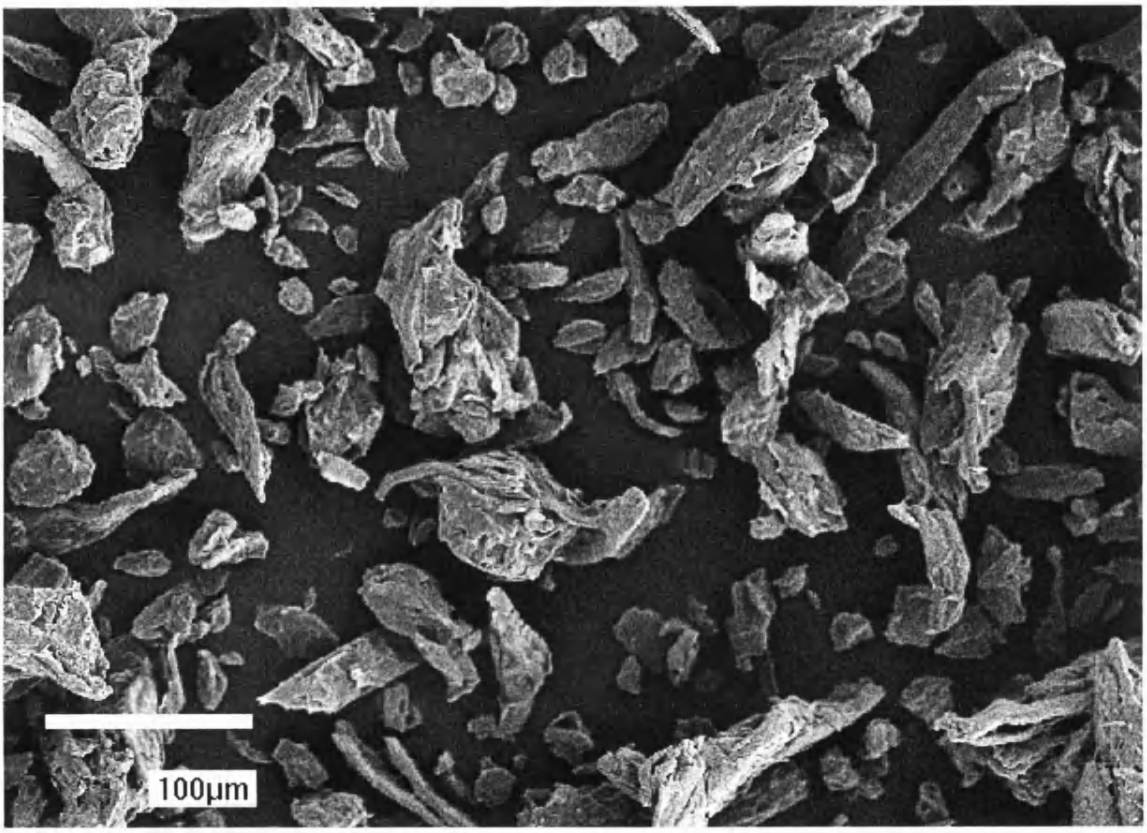



**Figure 2.5**. Scanning electron microscopy of Prosolv50M.

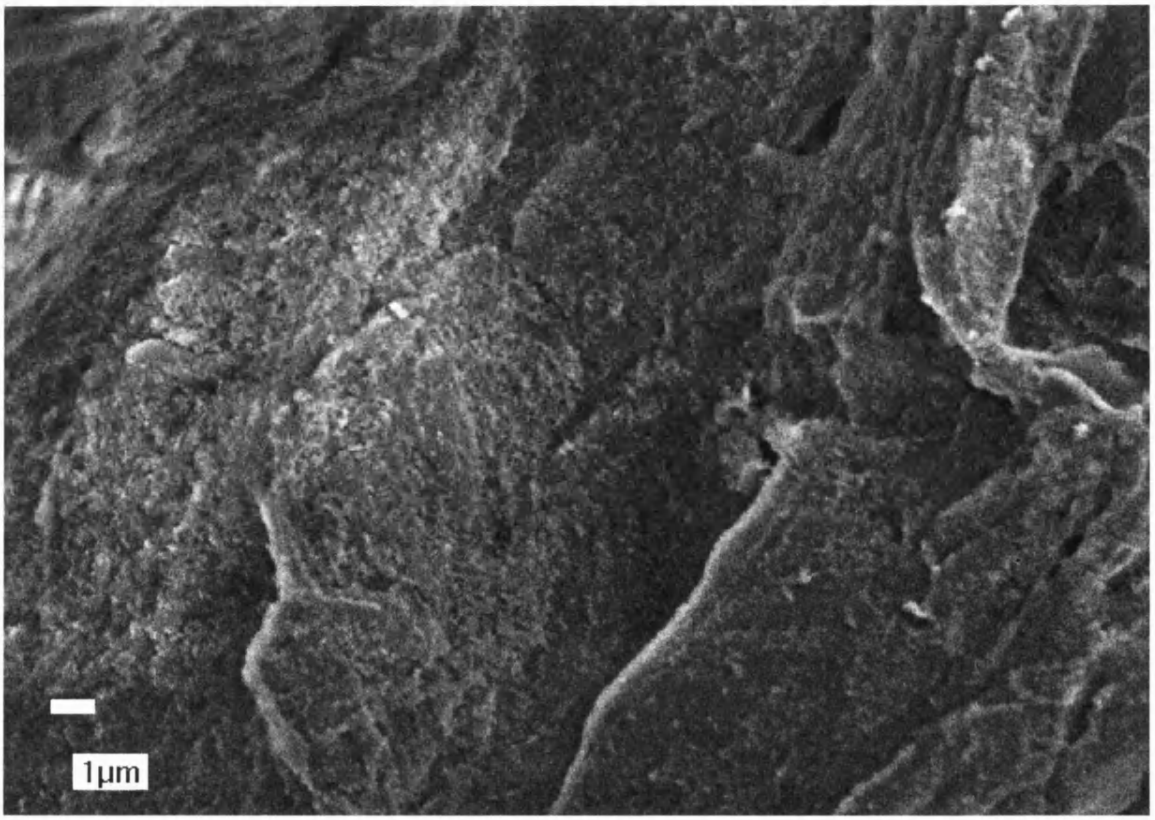



**Figure 2.6**. Scanning electron microscopy of Prosolv90M

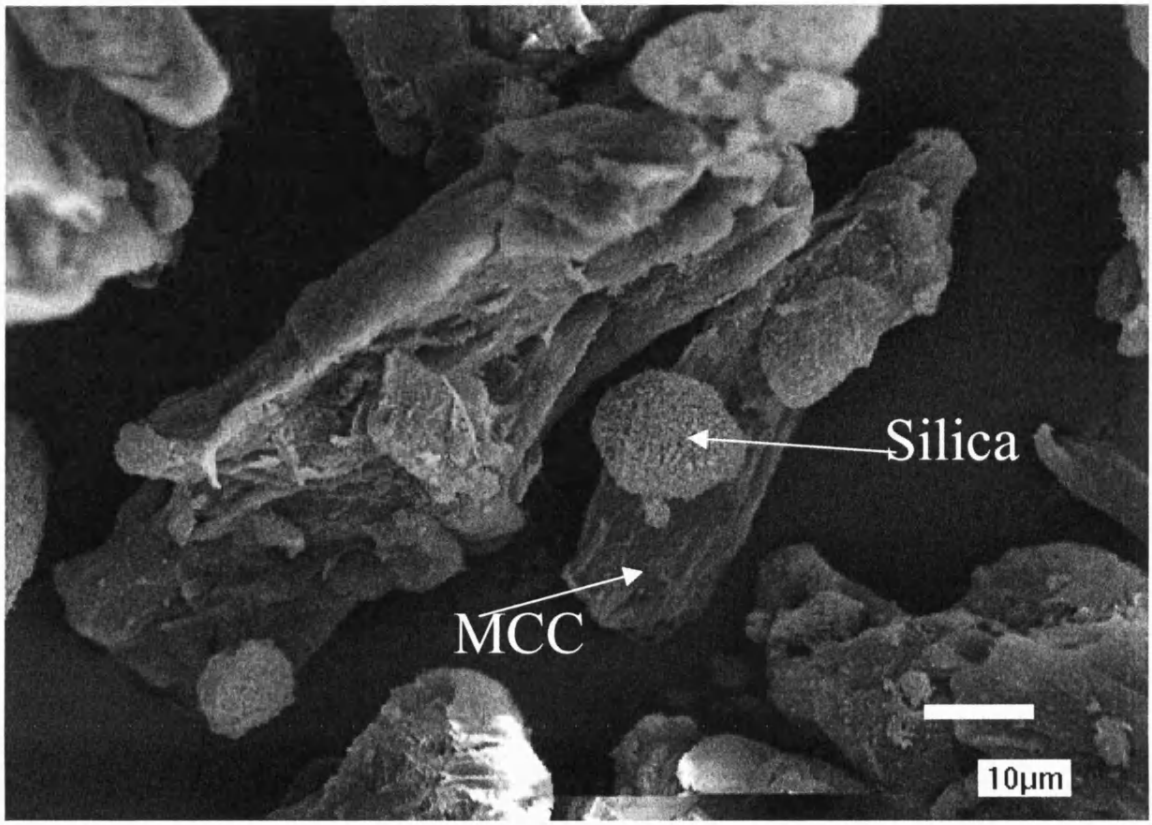



**Figure 2.7** Scanning electron microscopy of lab mix 50M. Emcocel 50M and colloidal silica 2% (w/w).

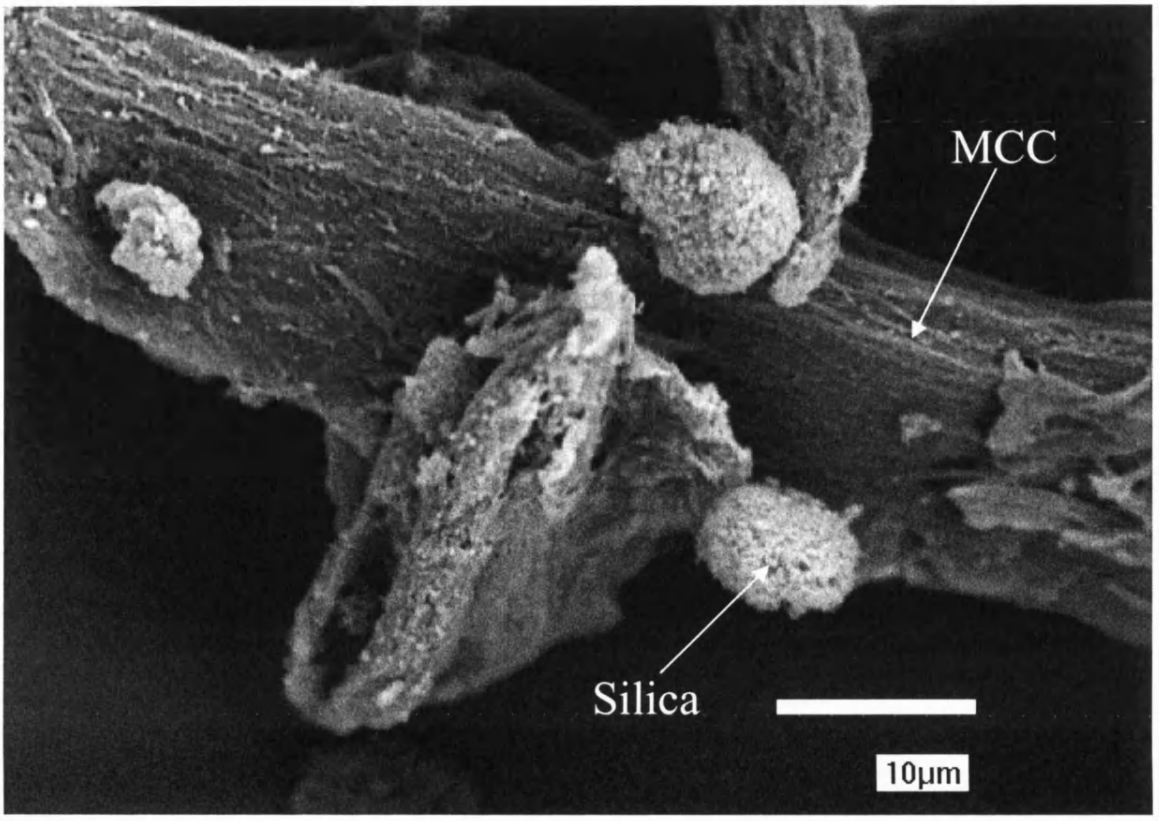



**Figure 2.8** Scanning electron microscopy of lab mix 90M. Emcocel 90M and colloidal silica 2% (w/w).

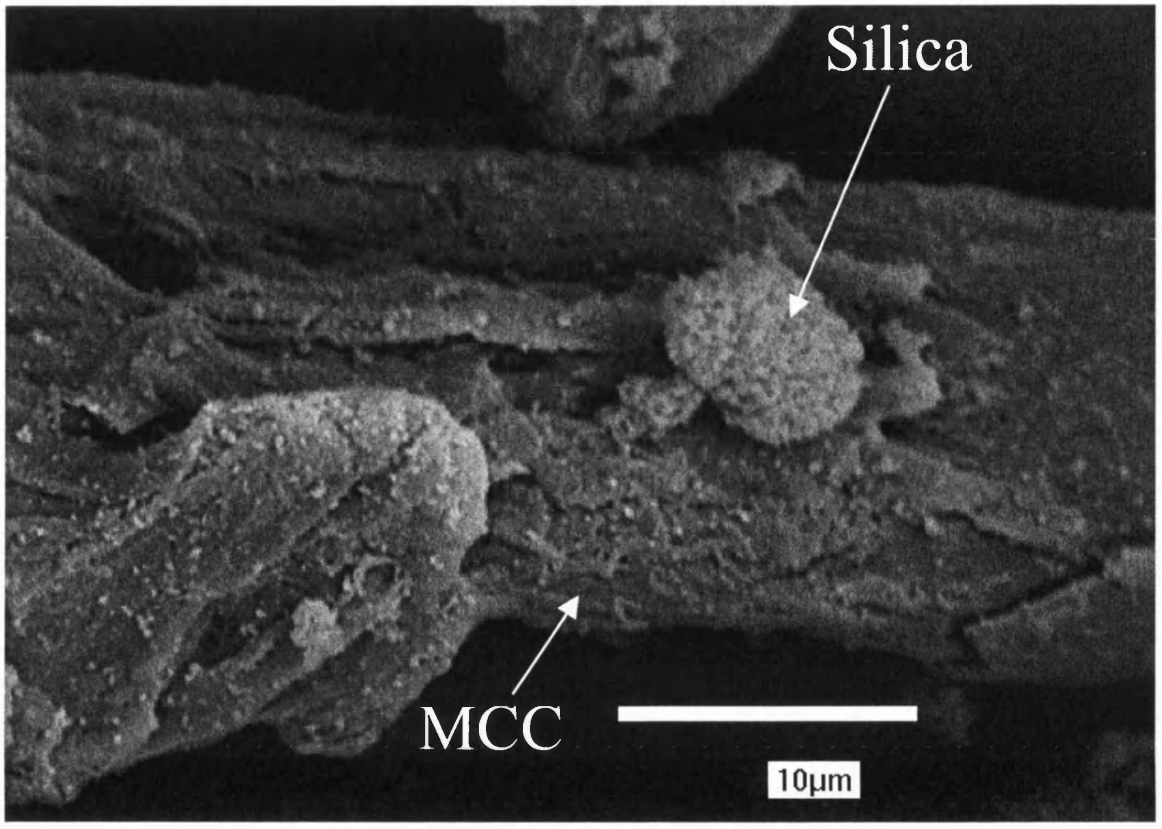



**Figure 2.9.** Scanning electron microscopy of lab mix 90M. Emcocel 90M and colloidal silica 2% (w/w).

### 2.3.6. Electrostatic charge

| Material | Metal Chute ($C.g^{-1}*10^{-9}$) n=10) | | Plastic Chute ($C.g^{-1}*10^{-9}$) (n=10) | | Treated Plastic Chute ($C.g^{-1}*10^{-9}$) (n=10) | |
|---|---|---|---|---|---|---|
| | Mean | S.D | Mean | S.D | Mean | S.D |
| Emcocel 50M | -0.199 | ±0.02 | +2.35 | ±0.64 | -9.23 | ±2.25 |
| Emcocel 90M | -3.47 | ±0.31 | +3.17 | ±0.88 | -10.11 | ±2.55 |
| Chlorpheniramine | -0.045 | ±0.02 | +1.98 | ±0.177 | -0.151 | ±0.055 |
| Aerosil 200 | -15.09 | ±4.95 | -38.86 | ±8.65 | - | - |
| Magnesium stearate | +1.91 | ±0.12 | -5.23 | ±0.69 | - | - |

**Table 2.6** Mean specific charge of powder sample contact with metal, plastic and treated plastic.

| State | Material |
|---|---|
| Electropositive | Microcrystalline cellulose |
| | Lactose D30 |
| | Emcocmpress200 |
| | Chlorpheniramine Maleate |
| Electronegative | Aerosil 200 |
| | Magnesium stearate |
| | |

**Table 2.7.** Show the triboelectric series constructed for different types of drug and excipient powders following flow in the plastic chute.

| State | Material |
|---|---|
| Electropositive | Magnesium stearate |
| | Emcocmpress200 |
| | |
| Electronegative | Microcrystalline cellulose |
| | Aerosil 200 |
| | Lactose D30 |
| | Chlorpheniramine Maleate |

**Table 2.8.** Show the triboelectric series constructed for different types of drug and excipient powders following flow in the metal chute.

Using data shown in Table 2.6, two triboelectric series were constructed for the same powders poured off a plastic chute (Table 2.7) and a metal chute (Table 2.8). The colloidal silica sample was found to become most electronegative following flow on both plastic and metal chutes. Magnesium stearate was the next most electronegative material when contacted with plastic, but became electropositive when contacted with metal. The same type of charge reversal occurred with all type of Emcocel, which charged electronegatively when contacted with plastic chute and electropositive with metal chute. It is thought that this adhesion may occur because of high particle charge: mass ratio, surface asperities, contact surface roughness, and particle deformation on substrate contact. Adhered material may reduce the frequency of particle-steel interactions and lead to increased particle-particle interactions, which may be responsible for producing a complex bipolar system and therefore affect the net charge (Bennett, 1999). In general, still very little information is available on the contact area involved with the charge accumulation/transfer process.

Colloidal silica (Aerosil 200) was found to have the largest charge magnitude corresponding to a charge of (-38.86 $C.g^{-1}*10^{-9}$) in plastic chute and (-15.09 $C.g^{-1}*10^{-9}$) in metal chute. The surface area value for Aerosil200 was approximately183 $m^2\ g^{-1}$. Powder having finer particle sizes might be expected to acquire higher magnitudes of charges due to an increased in the surface area facilitating contact electrification.

# Chapter 3

# Development and use of flow methods for characterising microcrystalline celluloses

## *3.1. Introduction*

The flow properties of powders are of critical importance to the successful production of pharmaceutical dosage forms. There are many industrial processes, which require powders to be moved from one location to another. This is achieved by many different methods including gravity feeding and mechanically assisted feeding (Aulton, 1988), as well as a number of new and developing methods (e.g. vacuum transfer).

Powders differ in their flowability due to the differences in the physical and mechanical properties. A powder with good flow properties flows by gravity without any assistance. However, powders with poor flowability need some assistance in order to change their behaviour. Techniques such as adding flow agents or other physical modifications may achieve improvements (Lantz, 1990). This difference in the flow of powders results in weight variation (and thus content differences) when the powder is compressed (in the case of tablets) or is filled into capsules.

Shapes and sizes of containers and particles can have some effects in the flow rates of the powder.

Different methods are normally used to measure the flow of powders, as outlined in the introduction. In this study, Aero-Flow and Flo-dex apparatus were used methods to evaluate the flow properties. In addition, coefficient of tablet weight variation, as an indirect method for assessing the flow (but with some direct relevance to the study), was

also measured to compare the flow properties of powders as measured by the Aero-Flow and Flo-dex apparatus.

## *3.2. Methods*

### 3.2.1. Dynamic Flow Measurements

#### *3.2.1.1. Spinning Riffler*

The spinning riffler was used to obtain a more representative sample of powder (Kaye, 1995). It is based upon the principle that if one has an efficient mixer, then any portion of powder taken from the powder population homogenised in the mixer is a representative sample. This apparatus consists of a powder hopper with a control valve mounted over a rotating wheel. The wheel is divided into a set of test tubes. In operation, the control valve is opened and powder flows from the hopper into the test tube as the drive shaft rotates the wheel. Each tube passes under the hopper to obtain a sample (Kaye, 1995).

#### *3.2.1.2. Aero-Flow Apparatus*

Powder flowability was analysed using the Aero-Flow powder avalanching analyser (Amherst Process Instruments, Tewkesbury, UK). For more details see fig. 3.1. The powder was placed in a clear hollow perspex disc of 12cm diameter and 2cm depth. The disc was placed in a vertical position on the Aero-Flow, which rotates the disc at a constant speed of approximately 145 seconds per revolution. The edge of the disc was lined with a coarse grade of sandpaper (Garnet Cabinet Paper GCAB 60, Hermes 5 M 08). This was to ensure that measurements were due to avalanching and not slippage on the disc walls

(Kaye, 1997). To minimise the adhesion of the particles to the face of the perspex, the disc was sprayed with an anti-static spray. In order to decide on the best volume, which can give better flow measurements of powders, volumes of 25 and 50cm$^3$ collected from the spinning riffler were avalanched for 20 minutes.

As the disc rotates, the powder rotates with the disc until the powder reaches an unstable position. The Aero-Flow software records the avalanche time and creates a string of the interval time between the avalanches (Amherst Process Instruments, 1998). The Aero-Flow data are plotted on a discrete phase space map by defining the time between one set of subsequent avalanches and the time between the next subsequent avalanches. Each sample was measured five times and the average was then taken for each sample. For the purposes of this study fractal analysis of the results was not carried out but the mean time between avalanches, and the relevant standard deviation, were used as indices of flow.

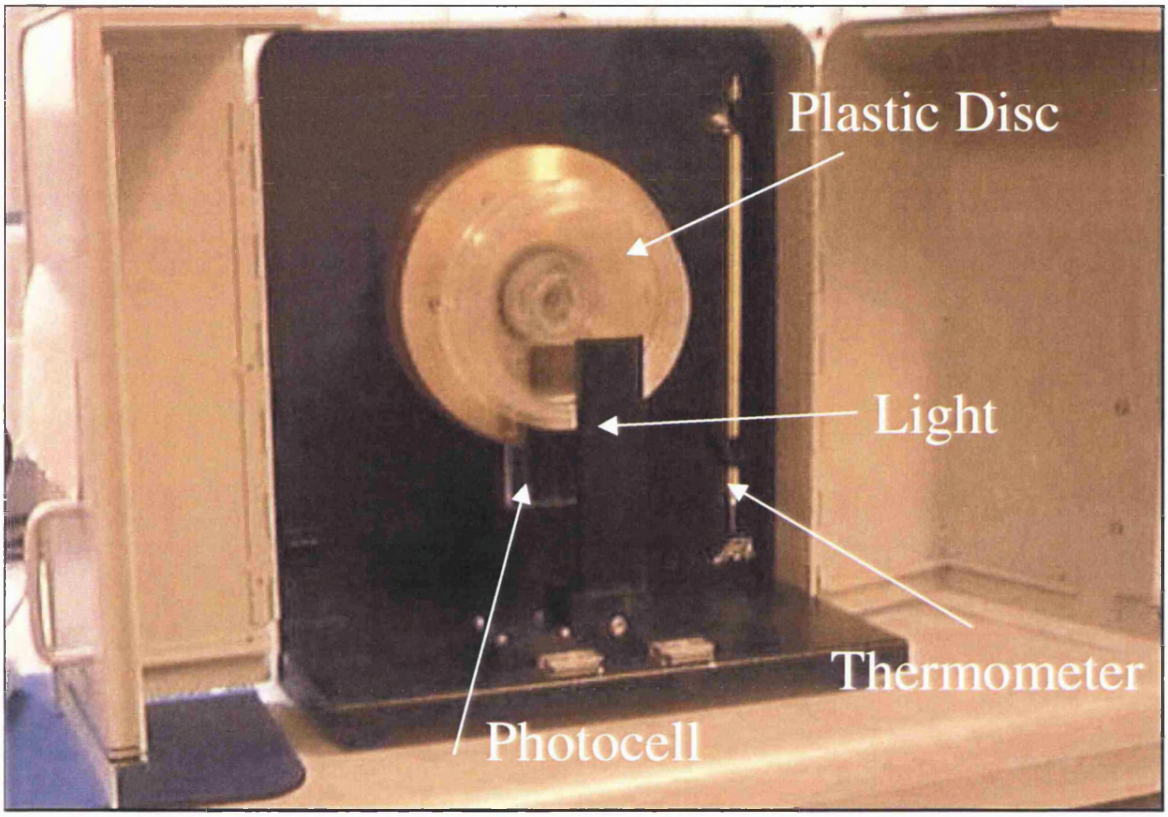



**Fig. 3.1.** Aero-Flow Apparatus.

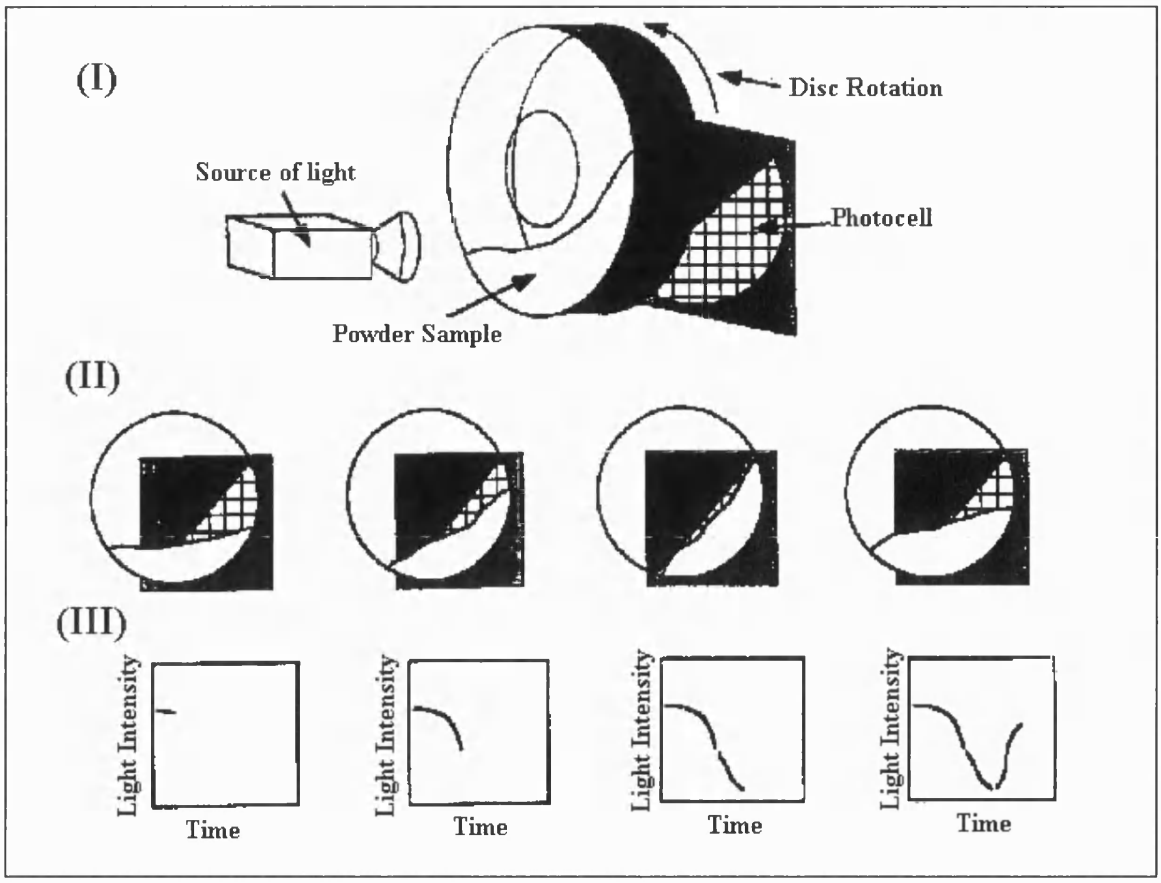



**Fig. 3.2.** Studying the Avalanching Behaviour of a Powder By Using Rotating Disc.

(I) The rotating disc avalanching equipment.

(II) The Progress of a single avalanche in the disc.

(III)Voltage output from the photocell as recorded by the computer.

(After Kaye, 1995)

Figures 3. 3. And 3. 4. show the difference between free flow powder and poor flow powder from the data and the strange attractor.

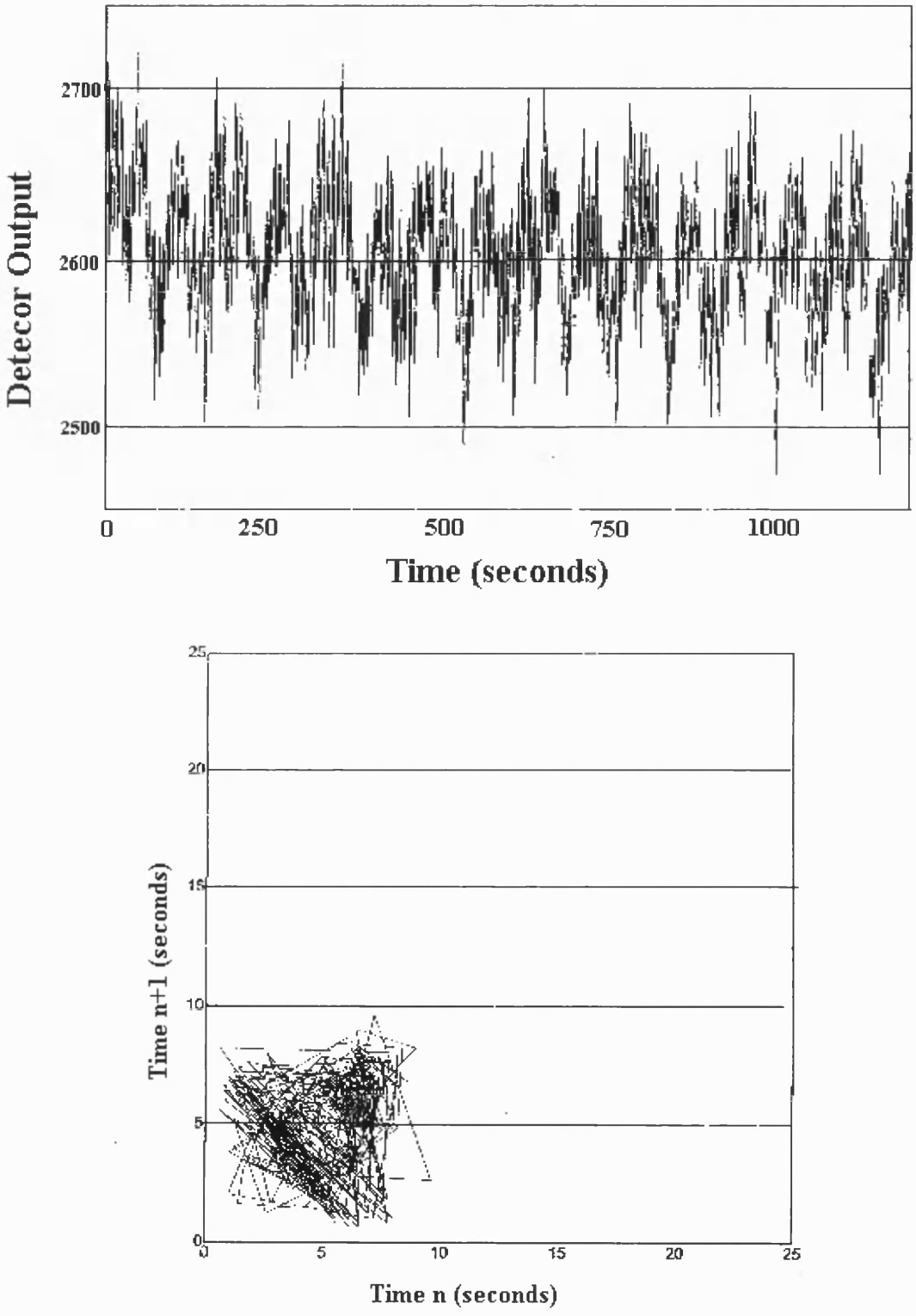
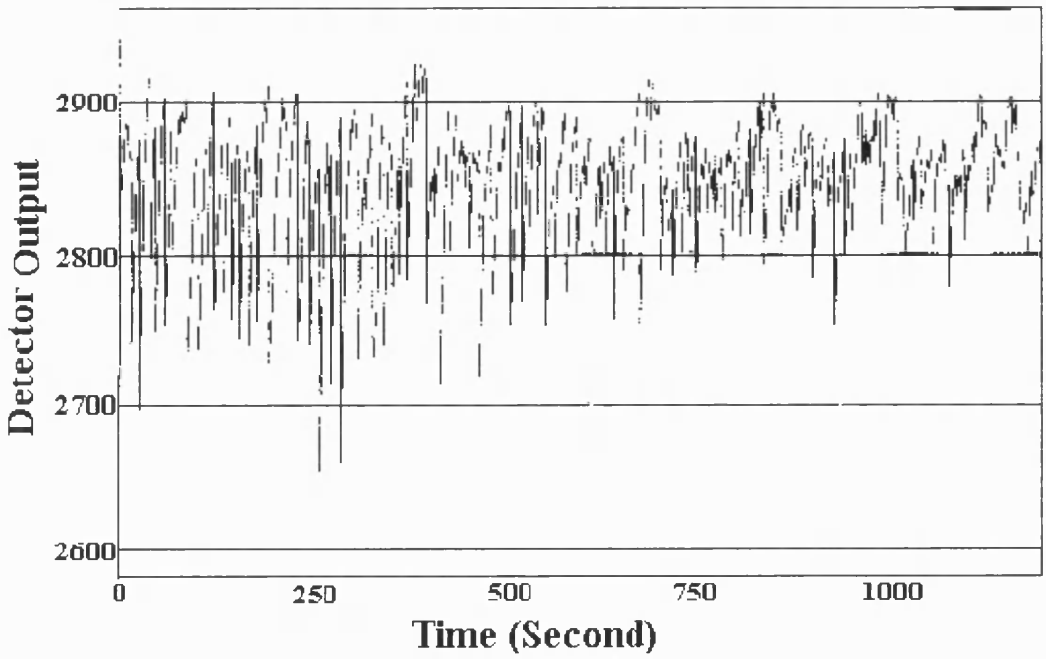



**Figure 3.3** Data and strange attractor for Prosolv 90M.



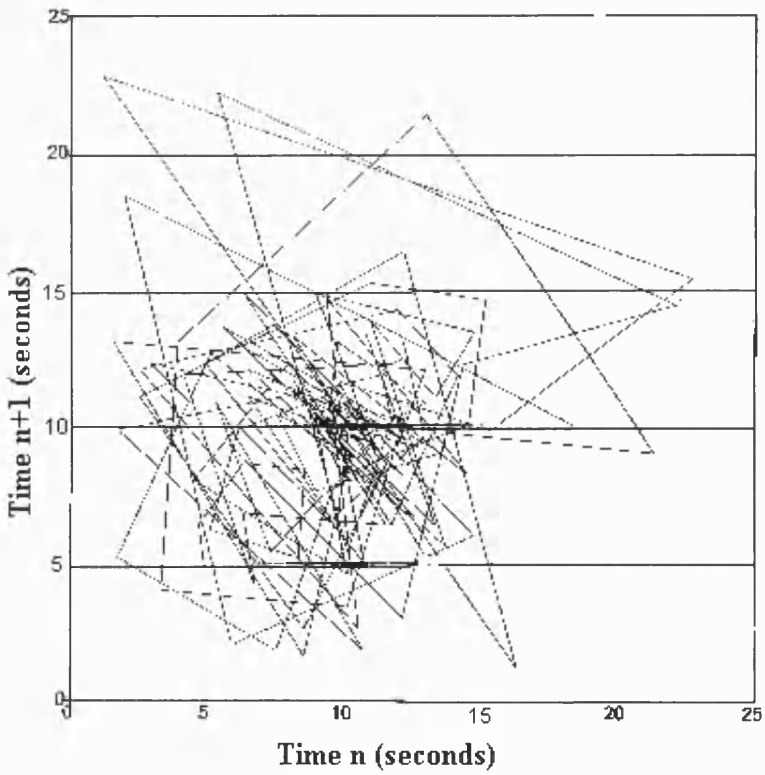




**Figure 3.4** Data and strange attractor for Emcocel SP15.

The Aero flow results are plotted on a discrete phase space map. The data is plotted by defining a point by the time between one set of subsequent avalanches and the time between the next set of subsequent avalanches. Thus if data set containing the time between avalanches (T1,T2,T3,T4,....) the first point will described by (T1,T2), the second point would be described by (T2,T3), the nth point would be described by (Tn,Tn+1). Each point is connected to the next point by a line. The resultant graph is often referred to a strange attractor pattern. The centred of the graph will lie along a 45° axis.

The avalanching behaviour of free flowing powders will produce a strange attractor with a centred close to zero and will exhibit a fairly tight attractor pattern as shown in figure 3.3.

The opposite was happened in figure 3.4 the avalanching behaviour of poor flow powder will produce a strange attractor with a centred far from zero and will show an expanded attractor.

*3.2.1.3. Hopper Flow Rate Measurements*

Hopper Flow Rate was measured using a Flo-dex apparatus (Flo-dex Powder Flowability Index Test Instrument, Hanson Research Corporation, Chatsworth, CA, USA). Approximately 30g of microcrystalline cellulose powders were used to fill the container to within 1cm or so from the top.

Powder was loaded carefully, tapping the bottom of the funnel lightly so that the powder is introduced into the receptacle cylinder without packing. After a minimum of 30

seconds from loading, the test was carried out to avoid any possible formation of flocculi (Flo-dex Operation manual). For powders not previously tested, the test was started with a 16mm orifice disc. The release lever was slowly turned until the closure drops and opened (whilst attempting to minimise vibration as this would cause the powder to fall freely through the orifice). The time taken for all the powder to leave the container was recorded, together with the mass of powder. The test is normally positive when it is possible to see the open hole at the bottom (Flo-dex manual).

The rate of flow can be measured by this equation:

$$\textit{Rate} \text{ of flow} = \frac{\text{Mass of powder passing through orifice}}{\text{Time for the powder to pass through the orifice}} \qquad \text{Equation 3 1}$$

In order to study the effect of relative humidity on the powder flow, dynamic flow experiments were carried out after exposing each powder to different conditions of relative humidity. Prior to the flow measurements, samples were exposed to a range of humidities (8%, 28%, 43%, 58% 72% and 93%) by sealing in vessels containing saturated salt solutions for a minimum of 48 hours.

### 3.1.1. Assessment of Intrinsic Physical Properties of Powders

#### *3.2.2.1. Uniformity of Tablet Weight*

Tablet weight variation was measured on a Manesty F3 single station tablet press (Manesty Machines Ltd., Liverpool, UK ) equipped with 8mm flat faced tooling. No lubrication of die or powders was required. Flow was by gravity feed. Target weight of tablets was approximately 100mg. 50 tablets were produced under normal production

conditions and weighed (Rubinstein, 1988). The relative standard deviation (RSD) of the weight was then calculated to be an indication of flow. This procedure was carried out after exposing the powder to different conditions of relative humidity. Prior to tablet formation, samples were exposed to a range of humidities (8%, 28%, 46%, 58%, 72%, and 93%) by sealing in vessels containing saturated salt solutions for a minimum of 48 hours.

## *3.3. Development of Methods*

### 3.3.1 The Effect of the Powder Volume on the Flow

In order to decide on the best volume, which can give better flow measurements of powders, two sets of experiments were carried out using different volumes of powder. Volumes of 25 and 50cm$^3$ were avalanched by using Aero-Flow apparatus as described in 3. 2. 1. 2.

### 3.3.2. The Effect of an Antistatic on Powder Flowability

Anti-static spray (RS Anti-static cleaner 569-284, RS components, Northants, (U.K) was used to evaluate the possible influence of static on adhesion to the perspex face of the Aero-Flow. To evaluate the effect of an antistatic on powder flow, volumes of 50cm$^3$ were avalanched with and without spraying the face of the Perspex with an antistatic as described in 3.2.1.2.

The anti-static cleaner contain (Sodium nitrate (0-1%), Propan-2-ol (5-10%), Ammonium Hydroxide (0-1%), Butane (1-5%) and Propane (1-5%).

### 3.3.3. Flow Properties of MCC and SMCC at Different Humidities

The flow properties of microcrystalline cellulose (Emcocel 50M, 90M, SMCC 50, 90M, (1% w/w colloidal silica), SMCC 50, 90M, (1.7% w/w colloidal silica), Prosolv 50, 90M, (2% w/w colloidal silica) and lab mix 50M, 90M, (2% w/w colloidal silica) were studied at different conditions of relative humidity. Samples were exposed to a range of different humidities (8%, 28%, 46%, 58%, 73%, and 92%) as described in 3.2.1.3. The flow the samples was evaluated using three different methods. Firstly, by measuring the avalanche time of each sample using Aero-Flow apparatus. The flow patterns were presented by plotting each relative humidity of every sample against its representative mean avalanche time (figures 3.5. and 3.6.). Secondly, using the Flo-dex to measure the flow rate of each sample as described in 3.2.1.3. Emcocel 50M and 90M series were measured at constant orifice of 22 mm. Each relative humidity of every sample was plotted against its representative flow rate (figures 3.7 and 3.8). Thirdly, by tablet weight variation method as described in 3.2.3.3. Each relative humidity of every sample was plotted against its representative RSD%. In an attempt to find a correlation between the mean avalanche time and RSD%(figures 3.9. and 3.10.).

The effect of adding 1%, 1.7% and 2% of colloidal silica (CS) to the 50M and 90M grades was also studied at different relative humidities. The mean avalanche time and RSD% were measured for each sample. The percentage of the added colloidal silica was plotted against the mean avalanche time and the RSD% for each humidity.

## *3.4. Results and Discussion*

### 3.4.1. The Effect of Powder Volume on Measurement of Mean Avalanche Time

Table 3.1 summarises the flow measurements of powders using volumes of 25 and 50ml. There is significant difference in flow measurements of powders using volumes of 25ml compared with the same powders using volumes of 50ml. Flow measurements using 50ml of powder had shown a real and an expected pattern of avalanches. Whereas avalanches using 25ml of powders had shown a slippage effect. Consequently, a powder volume of 50ml was chosen for all flow measurements. The addition of CS at a concentration of 1% to Emcocel 50M resulted in a significant improvement in powder flow as illustrated by the significant decrease in the mean avalanche time (from 9.88 s to 6.60 s). Interestingly, further increase in CS concentration (to 1.7%) resulted in an increase in the mean avalanche time. This seemingly anomalous effect of CS on mean avalanche time may be due to a "flooding" effect or excessive or abundant filling of void spaces by the glidant. CS enhances flowability by coating the host particles completely, smoothing irregularities in their shape and reducing the frictional and adhesive forces that operate between them. However as both these materials were investigational materials, the exact properties of which were not precisely known, some caution should be exercised in analysing these results too closely. Further discussion of this possible effect is outlined in section 3.4.2. Emcocel 90M showed superior flow properties compared to Emcocel 50M and that was true at all CS concentrations investigated. As shown in table 2.3 Emcocel 90M has a mean particle size ($d50^{th}$) of about 100 μm whereas Emcocel 50M has a particle size of approximately 65 μm. Such difference in particle size is the reason for such difference in flow between the two grades of Emcocel. When the particles are larger, the

gravitational force, which increases with the cube of the diameter, becomes much greater, although the attraction may be smaller, since a close approach cannot be readily achieved.

| Name of Sample | Sample with 25ml | | Sample with 50ml | |
|---|---|---|---|---|
| | Average Mean avalanche time (s) | Standard deviation | Average Mean avalanche time (s) | Standard deviation |
| Emcocel 50M | 9.88 | ±1.12 | 6.00 | ±0.293 |
| Emcocel 50M 1% | 6.60 | ±0.229 | 6.42 | ±0.334 |
| Emcocel 50M 1.7% | 7.7 | ±0.605 | 6.93 | ±0.244 |
| Emcocel 90M | 6.90 | ±0.453 | 5.32 | ±0.865 |
| Emcocel 90M 1% | 5.33 | ±0.212 | 5.05 | ±0.144 |
| Emcocel 90M 1.7% | 5.20 | ±0.378 | 8.07 | ±0.613 |
| Emcocel HD 90 | 5.87 | ±0.544 | 5.59 | ±0.254 |
| Emcocel WG 50M | 5.90 | ±0.497 | 5.00 | ±0.558 |
| Emcocel WG 90M | 4.80 | ±0.359 | 4.59 | ±0.223 |
| Emcocel LP200 | 5.20 | ±0.440 | 5.19 | ±0.402 |
| Emcocel SP15 | 13.1 | ±1.23 | 10.3 | ±1.70 |
| Avicel PH105 | 13.1 | ±0.768 | 10.8 | ±0.804 |
| Avicel PH200 | 4.93 | ±0.469 | 5.23 | ±0.560 |

**Table 3.1** Comparison between the mean avalanche time for samples using volumes of 25 and 50 ml of powder.

Overall, the results obtained (particularly the 50ml sample results) showed an expected pattered of flow for these grades of microcrystalline celluloses especially when the antistatic was used. Particularly interesting was the fact that 'equivalent' grades of material from different suppliers demonstrated very similar results. For instance the results for the large particle size microcrystalline celluloses Emcocel LP200 (5.19±0.402s) and Avicel PH200 (5.23±0.560s) were of a very similar magnitude, as were the results for the small particle size materials Emcocel SP15 (10.31±1.70s) and Avicel PH105 (10.80±0.804s). This gave considerable confidence that the results had some validity.

### 3.4.2. The Effect of an Antistatic Spray

During the first set of experiments it was observed that most of the powders tested using the Aero-Flow were sticking to the disc and were apparently cohesive in nature. This problem had the effect of obscuring the disc (a problem for a technique that relies on light transmission for results) and reduced the overall amount of powder avalanching. The adhesion may reflect an increase in interparticle forces due to the generation of electrostatic charges. It was thought that it would be beneficial to minimize the electrostatic charge interference by using an antistatic agent. As mentioned above the anti-static ('Clearance') was used as antistatic agent in the present work. The effect of the antistatic agent was shown to be helpful in illustrating the effect of CS in improving the flow of different powders investigated in this study. As shown in Table 3.2. before addition of the antistatic agent, increasing CS concentration adversely affected powder flow as represented by the increase in the avalanche time. However, following the use of the antistatic agent such increase in CS concentration (1 to 1.7% w/w) resulted in improvement of powder flow. Moreover, the seemingly anomalous results of a higher avalanche time for Emcocel 90M 1.7% than for Emcocel 50M 1.7% (8.07s and 6.93s, respectively) were reversed after the addition of the antistatic spray (4.65s and 6.07s, respectively). Although one must be careful about seizing on the 'correct' or 'desired' result as a validation of the method this result seems important.

This general trend of standardised results was true for all other determinations (Table 3.2.). It was shown by Orband and Geldart 1995 that the use of small quantities of Larostat 51 helped when standardising flow properties such as bulk densities and Hausner ratios as well as the behaviour of the samples exposed to various controlled relative humidities.

The anti-static spray was used in all subsequent experiments. In addition further techniques were used to try and minimise problems related to electrostatic charge (for

instance, following washing the perspex disc was air dried in an oven rather than towel dried).

| | Sample of 50ml without antistatic spray | | Sample of 50ml with antistatic spray | |
|---|---|---|---|---|
| Name of Sample | Average Mean avalanche time (s) | Standard deviation | Average Mean avalanche time (s) | Standard deviation |
| Emcocel 50M | 6.00 | ±0.293 | 8.02 | ±0.598 |
| Emcocel 50M 1% | 6.42 | ±0.334 | 6.74 | ±0.304 |
| Emcocel 50M 1.7% | 6.93 | ±0.244 | 6.07 | ±0.365 |
| Emcocel 90M | 5.32 | ±0.865 | 5.63 | ±0.492 |
| Emcocel 90M 1% | 5.05 | ±0.144 | 5.32 | ±0.865 |
| Emcocel 90M 1.7% | 8.07 | ±0.613 | 4.65 | ±0.711 |
| Emcocel HD 90 | 5.59 | ±0.254 | 5.57 | ±0.562 |
| Emcocel WG 50M | 5.0 | ±0.558 | 6.31 | ±1.13 |
| Emcocel WG 90M | 4.59 | ±0.223 | 5.66 | ±0.424 |
| Emcocel LP200 | 5.19 | ±0.402 | 4.81 | ±0.245 |
| Avicel PH200 | 5.23 | ±0.56 | 4.31 | ±0.803 |

**Table 3.2** The flow measurements for samples with and without an anti-static spray using volume of 50ml of powder.

### 3.4.3. Effect of Relative Humidity on Flow Properties of Different Powder Mixes Investigated at Different Levels of CS

In this experiment the newly available material Prosolv (commercial silicified microcrystalline cellulose, 2% colloidal silica content) and a lab mix to the same proportions were also tested.

The effect of relative humidity on the flow of different powder mixes containing Emcocel 50M is shown in figure 3.5. The figure also shows the effect of different concentrations of CS on the powder flow. No significant change in avalanche time at lower relative humidities (8% to 28%). At lower relative humidities of <28%, contact electrostatic charges build up to a maximum level. Whereas at higher relative humidities of >84% condensation of water, formation of liquid bridges and capillary bonds occur (Coelho and Harnby, 1979). This explains the increase in the avalanche time (i.e. poor flow) at high relative humidity of 93%. An optimal relative humidity exists at 43% where optimum flow was observed for most of the powders investigated. The effect of CS concentration is evident where an increase in its concentration results in significant decrease in the mean avalanche time. There is also a significant difference between the results obtained for Prosolv50M (which contains 2% w/w colloidal silica co-processed) and a 2% lab mix of Emcocel 50M and colloidal silica. The reasons for this are discussed later in section (3. 4. 6). It would appear that, in addition to improving overall flow the presence of colloidal silica has the beneficial effect of reducing the influence of humidity on the observed results, with Prosolv50M and the lab mix being almost completely unaffected by humidity.

A similar trend in powder flow to that observed for powder mixes containing Emcocel 50M was recorded for powder mixes containing Emcocel 90M as shown in fig 3.6. However, powder mixes containing Emcocel 90M exhibited better flow properties as

compared to those observed for powder mixes containing Emcocel 50M. Such difference in flow properties may be explained on the basis of particle size differences between Emcocel 50M and Emcocel 90M. Emcocel 90M has a particle size of approximately 90-100 μm whereas Emcocel 50M mean particle size is approximately 65 μm. At a particle size approaching 100 μm the effect of gravitational forces will be greater than cohesive and adhesive surface forces including electrostatic forces. The opposite is true when the particle size is reduced below 100 μm where the cohesive and adhesive will become greater than the gravitational forces. That will impact the mechanical properties of powders including flow as explained above.

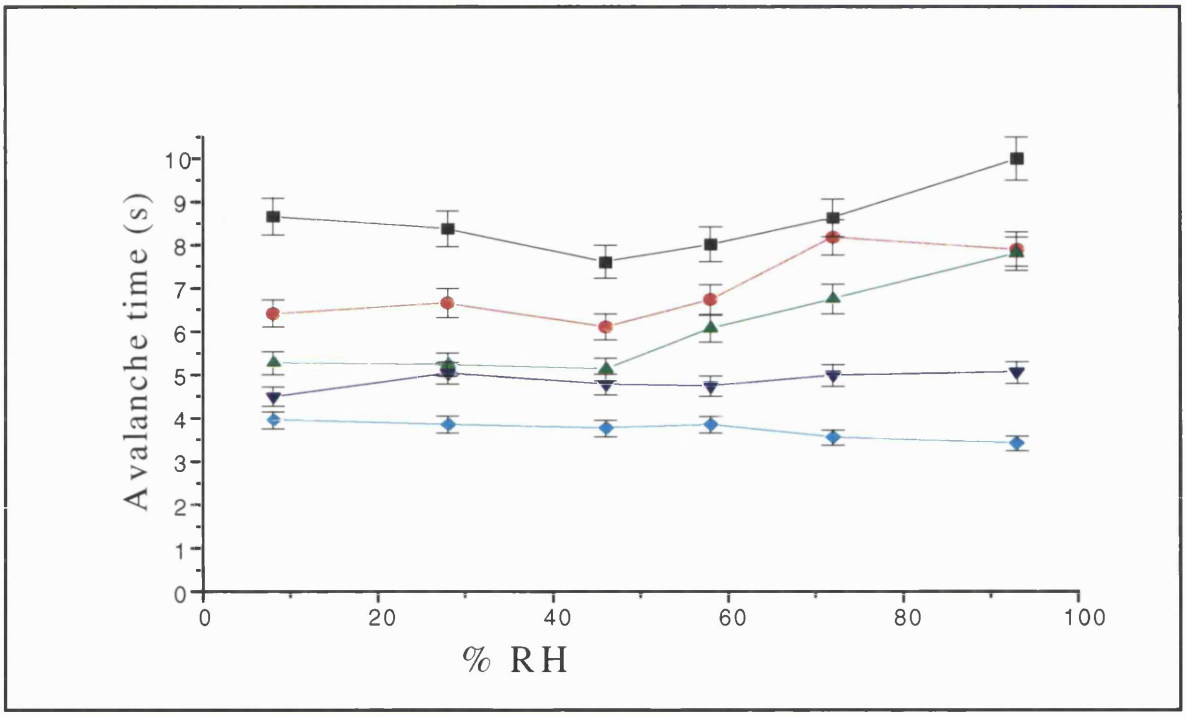



**Fig. 3.5** Influence of different relative humidities on mean avalanche time for Emcocel 50M (■), presence of 1% colloidal silica (●), presence of 1.7% colloidal silica (▲), presence of 2% colloidal silica (Prosolv50M) (▼), and lab mix 2% colloidal silica (♦).

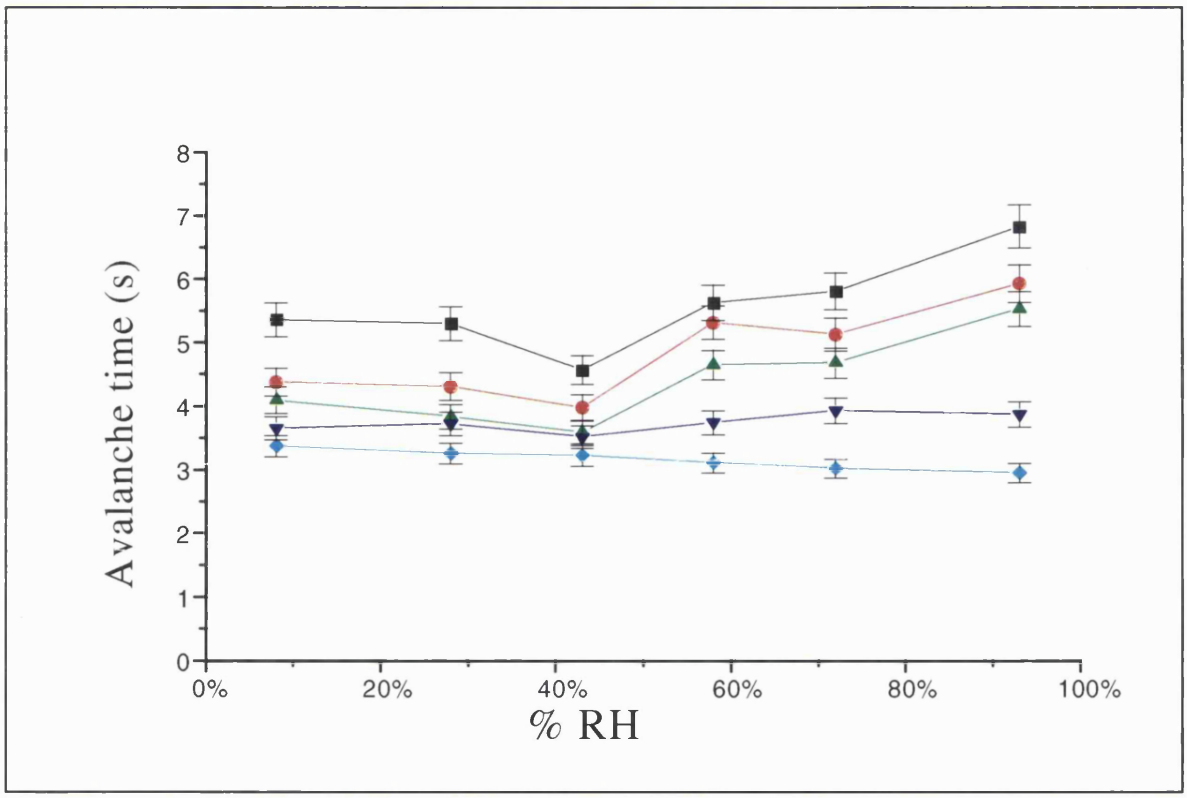



**Fig. 3.6** Influence of different relative humidities on mean avalanche time for Emcocel 90M (■), presence of 1% colloidal silica (●), presence of 1.7% colloidal silica (▲), presence of 2% colloidal silica (Prosolv90M) (▼), and lab mix 2% colloidal silica (♦).

As it can be seen from figs 3.5 and 3.6. the avalanche times for Emcocel 50M and Emcocel 90M either alone or in presence of 1%, 1.7%, 2% (Prosolv) and 2% lab mix colloidal silica were lower at relative humidity of 43%. However, there was an increase in the mean avalanche time at humidities greater than 43% exception to this tendency is a noted decrease of avalanche times for the 2% lab mix at relative humidities 72% and 93% where there was a decrease in avalanche time. However, this decrease was not significant compared with the avalanche time at 43%.

The presence of colloidal silica in all concentrations tested seemed to decrease the avalanche time in both Emcocel 50M and 90M. The avalanche time when using 90M Emcocel was significantly less than that of Emcocel 50M ($P<0.05$).

The presence of increased concentrations of colloidal silica at 43% relative humidity produced concentrations related decreases in avalanche times. For example the presence of 1.7% and 2% silicon dioxide produced significant reductions in avalanche times compared with 1% silicon dioxide. Thus, the presence of silicon dioxide seamed to enhance flowability for Emcocel.

The presence of 1.7% colloidal silica at relative humidity greater than 43% increased the avalanche time. This increase in avalanche time was significantly greater in case of Emcocel 50M compared to Emcocel 90M ($P<0.05$). In case of other concentrations of colloidal silica 1%, and 2% (Prosolv) there were no consistent and gradual increases in avalanche time at relative humidity greater than 43%.

These results show that the presence of colloidal silica enhance the flowability at relative humidity 43%. The best flowability was observed in presence of 2% colloidal silica.

Generally, the use of Emcocel 90M at relative humidity 43% produced significantly better flowability compared with Emcocel 50M.

As mentioned earlier powder flow was also measured using a flow through hopper technique (Flo-Dex). Data generated for the powder mixes containing Emcocel 50M are shown in figure 3.7. Data indicated that Emcocel 50M (contains 1.7% w/w CS) exhibited optimal flow rate compared to the other powder mixes (Emcocel 50M and Emcocel 50M 1% CS) particularly at RH of 43%. However, using this technique, the differences were not shown to be distinct among the three powder mixes. Moreover, this technique might give ambiguous results for the powder mixes tested. At higher RHs (> 43%) the flow rate

was shown to increase. This indicates improvement in powder flow. However, it was shown earlier and for the same powders tested that the mean avalanche time, using the Aero-flow system, increased at higher RHs, which indicate a decrease in powder flow. As explained above, at elevated RHs moisture bonding may predominate leading to the formation of attractive capillary forces which enhance cohesion and adhesion of particles, thereby adversely affecting powder flow.

An explanation of the apparent differences between the two techniques may also be an indication of measuring slightly different properties in the material. It is possible that bridging (as measured by the Flo-dex but not the Aero-Flow) may be influenced much more by humidity.

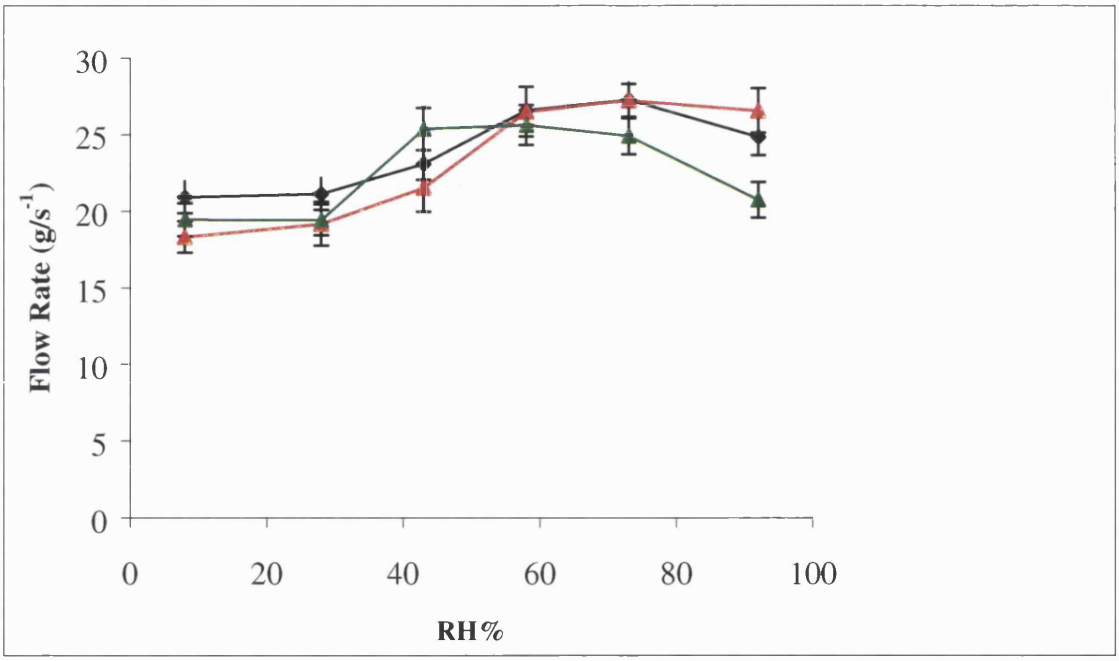



**Fig. 3.7.** Influence of different relative humidities on avalanche time for Emcocel 50M (♦), presence of 1% colloidal silica (▲), presence of 1.7% colloidal silica (▲), by using Flo-dex.

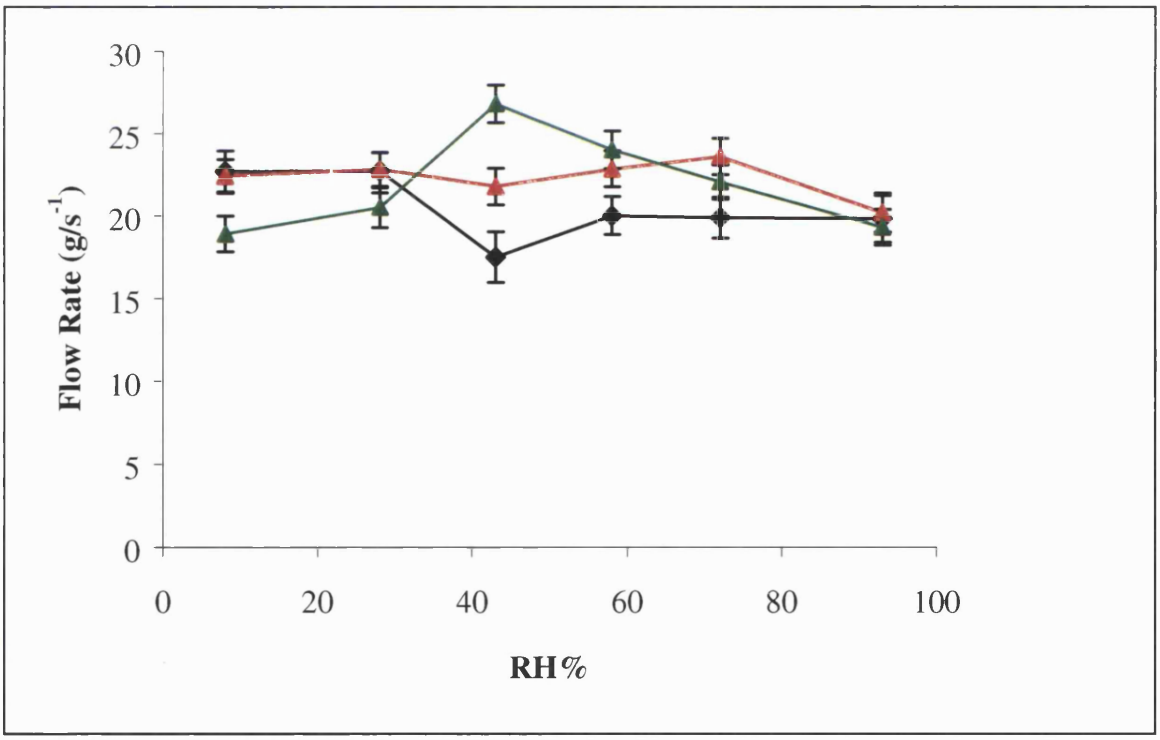



**Fig. 3.8** Influence of different relative humidities on avalanche time for Emcocel 90M (♦), presence of 1% colloidal silica (●), presence of 1.7% colloidal silica (▲), by using Flo-Dex.

Figure 3.7 and 3.8. show the effect of different RHs on the flow rate of different powder mixes containing Emcocel 50M and 90M.

The flow rate of powders containing Emcocel 90M is show better flow than mixes containing Emcocel 50M. The difference in particle size between the two grades of Emcocel (50M and 90M) is the main reason for such significant difference in flow properties for the mixes investigated. The difference in flow rate between the powder mixes tested was evident. Addition of CSD to Emcocel 90M resulted in a significant improvement in powder flow. Emcocel 90M containing 1.7% CS showed better flow rate than the other two powder mixes investigated (Emcocel 90M and Emcocel 90M 1%CS), whereas Emcocel 90M 1% CS has better flow rate than Emcocel 90M. This is in agreement with the results generated using Aero-Flow system described above

### 3.4.4. Valuation of Flow by Tablet Weight Variation Method at Different Humidities

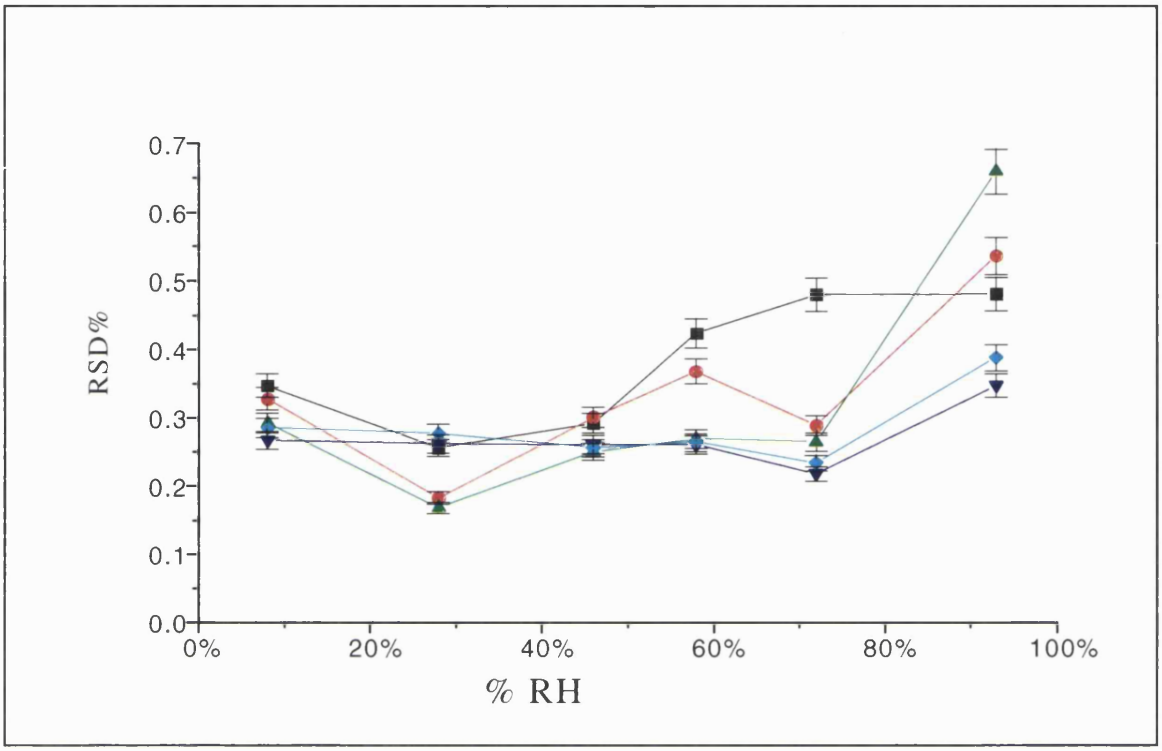



**Fig. 3.9** Influence of different relative humidities on tablet weight variation for Emcocel 50M (■), Presence of 1% colloidal silica (●), Presence of 1.7% colloidal silica (▲), Presence of 2% colloidal silica (Prosolv50M) (▼), and lab mix 2% colloidal silica (♦).

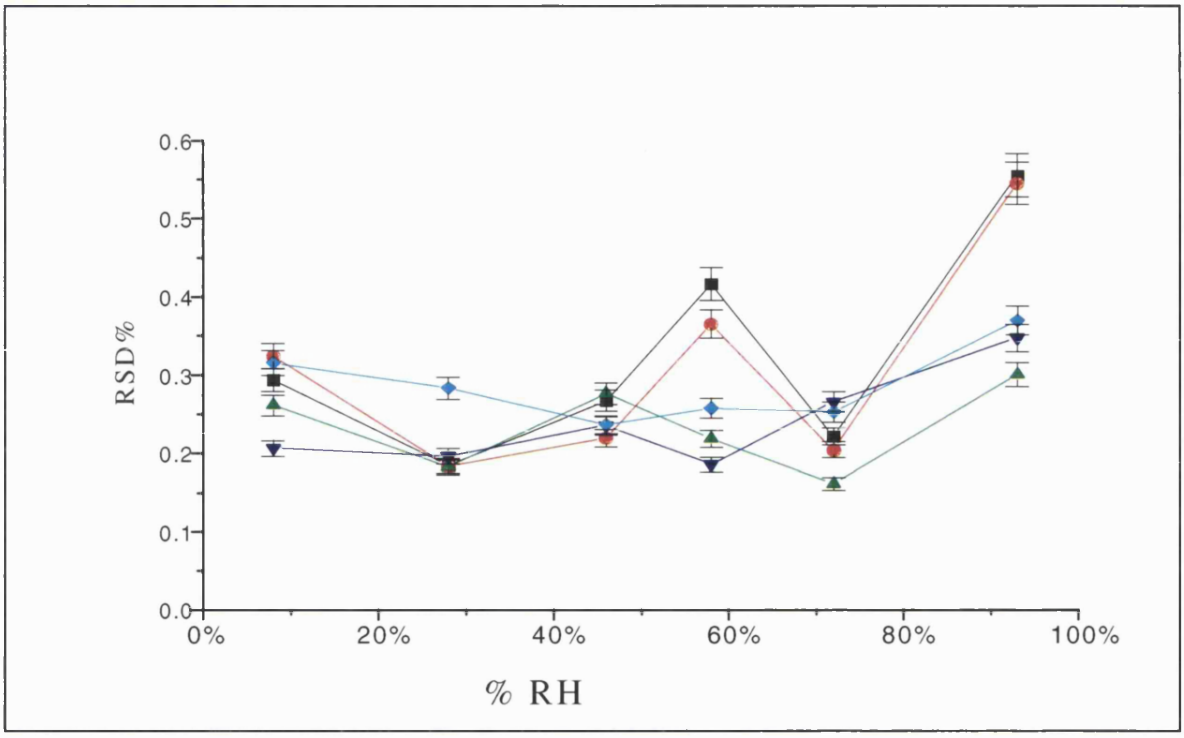



**Fig. 3.10** Influence of different relative humidities on tablet weight variation for Emcocel 90M (■), Presence of 1% colloidal silica (●), Presence of 1.7% colloidal silica (▲), Presence of 2% colloidal silica (Prosolv50M) (▼), and lab mix 2% colloidal silica (♦).

Tablet weight variations can be used as an indirect parameter to evaluate powder flow properties. In general, an optimal powder flow rate results in minimal tablet weight variation for a given product. In addition to processing factors during tableting including hopper and chute design, equipment geometry etc, powder flow represents the main factor to be considered to develop a robust and consistent product.

Therefore, it was thought that it would be beneficial to study the interrelationship between powder flow and tablet weight variation. This section of this chapter deals with investigating factors that affect tablet weight variation and associate such effect with that

tested earlier for powder flow. Figures 3.9 and 3.10 show the effect of different RHs on the weight variation of tablets prepared using binary powder mixes containing Emcocel 50M and Emcocel 90M, respectively. As shown in these figures RHs between 28% and 43% represent optimal conditions where minimal tablet weight variations were recorded. This is true for most powder mixes investigated which contain different grades of Emcocel. For both sets of powders Emcocel 50M or Emcocel 90M further increase in RH (>43%) caused an increase in tablet weight variation. This confirms results generated by the Aero-Flow system where it was found that an increase in RH caused significant increase in the mean avalanche time which indicates a decrease in flow rate of the powders tested.

However, as mentioned earlier, the adverse effect of elevated RHs on flow was not captured using the hopper flow measurement technique (Flo-Dex) as was shown earlier in figures 3.7 and 3.8.

With regard to Emcocel 50M alone, and in the presence of 1% and 1.7% colloidal silica at RH greater than 28%, there were clear tablet weight variation increases. Whereas at RH 72% there was a decrease compared with that observed at RH 58%. With regard to Prosolv50M and 2% lab mix colloidal silica there were a gradual decrease with increase in relative humidity from 8% to 72% RH. The tablet weight variation increased in both cases at RH 93%. While for Emcocel 90M alone, and in the presence of 1% colloidal silica at relative humidity greater than 28%, there was an increase in tablet weight variation with an increase in RH except at 72% in both cases where a decrease was noted compared with that at RH 58%. Also for 1.7% and Prosolv at RH above 28% there were an increase in tablet weight variation with increase in RH except at RH 58% a decrease was noted compared with that at 43%. Another decrease in tablet weight variation was noted at RH 72% in case of 1.7% colloidal silica. Regard with to 2% lab mix there were no consistent decreases or increases in tablet weight variations with increase in RH.

Generally, minimal tablet weight variation in all cases was observed at RH 28%. From statistic all point of view the presence of 1.7% colloidal silica produced the least tablet weight variation in case of 50M and 90M Emcocel.

Thus, the results showed that minimal tablet weight variation was observed at 28% and in the presence 1.7 % colloidal silica. With regard to particle size the 90M Emcocel produced greater tablet weight variation at RH 28% in presence of 1.7 % colloidal silica.

### 3.4.5. Use of the Aero-Flow in measuring flow of pharmaceutical powder mixes containing different levels of colloidal silica (CS)

Figure 3.11 shows the effect of colloidal silica (CS) concentration (%w/w) on the mean avalanche time (s). It also indicates weight variation of tablets prepared from such powder mixes at a relative humidity (RH) of 8%. As in the figure the increase in CS concentration resulted in a significant improvement in powder flow as represented by the decrease in the mean avalanche time. Such improvement in powder flow was matched by an improvement in tablet weight variation. Interestingly, while the improvement in powder flow or the decrease in mean avalanche time was shown to be significant the weight variation between the tablets was slightly different. This proves that the Aero-Flow device was very sensitive in detecting seemingly slight differences in the flow of powder mixes. Figure 3.12 shows the effect of colloidal silica (CS) concentration (%w/w) on the mean avalanche time (s) and weight variation of tablets prepared from such powder mixes at a relative humidity (RH) of 28%. As the figure shows the increase in CS concentrations resulted in a significant improvement in powder flow as represented by the decrease in the mean avalanche time. This follows the trend for the other previously described examples (e.g. at 8% RH). Figures from 3.13-3.16 show the effect of colloidal silica (CS) concentration

(%w/w) on the mean avalanche time (s) and weight variation of tablets prepared from such powder mixes at RHs of 43%, 58%, 72% and 93%, respectively. As these figures show the increase in CS concentration resulted in a significant improvement in powder flow as represented by the decrease in the mean avalanche time at all such elevated RHs. As shown for lower RHs the effect of CSD on powder flow was better illustrated using mean avalanche time than using tablet weight variation.

Figure 3.17 shows the effect of colloidal silica (CS) concentration (%w/w) on the mean avalanche time (s) and weight variation of tablets for Emcocel 90M series prepared from such powder mixes at different relative humidities (RHs) of 8%. As the figure shows the increase in CS concentration resulted in a significant improvement in powder flow as represented by the decrease in the mean avalanche time. Such improvement in powder flow was matched by an improvement in tablet weight variation. Interestingly, while the improvement in powder flow or the decrease in mean avalanche time was shown to be significant the weight variation between the tablets was slightly different. It showed an increase with the increase of (CS). This follows the trend for the other previously described examples (e.g. at 8% RH). Figures from 3.18-3.22 show the effect of colloidal silica (CS) concentrations (%w/w) on the mean avalanche time (s) and weight variation of tablets prepared from such powder mixes at RHs of 43%, 58%, 72% and 93%, respectively.

Generally, the presence of colloidal silica in different concentrations tested seemed to decrease the avalanche time in both Emcocel 50M and Emcocel 90M and the avalanche time when using Emcocel 90M was significantly less than that of 50M Emcocel ($P<0.05$).

As a conclusion the presence of 1.7% colloidal silica produced the least tablet weight variation in case of Emcocel 50M and Emcocel 90M at RH 28%.

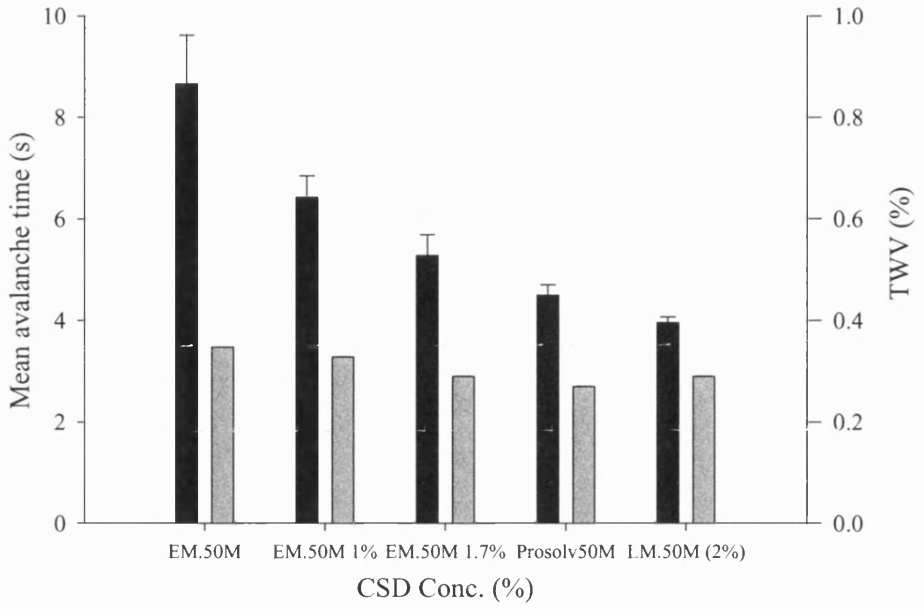



**Fig. 3.11.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 8%) for Emcocel 50M series. Mean avalanche time ▮ and tablet weight variation ▮.

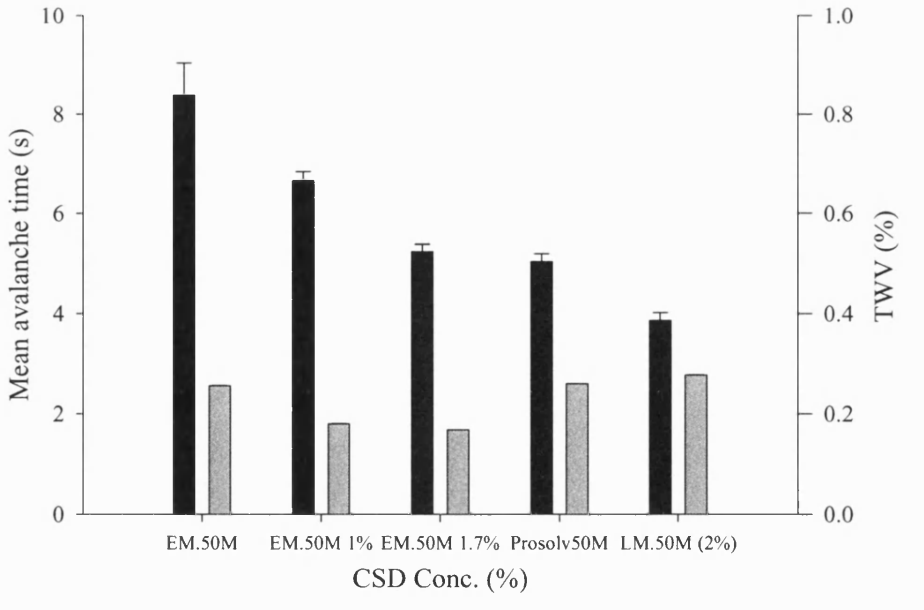



**Fig. 3.12.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 28%) for Emcocel 50M series. Mean avalanche time ▮ and tablet weight variation ▮.

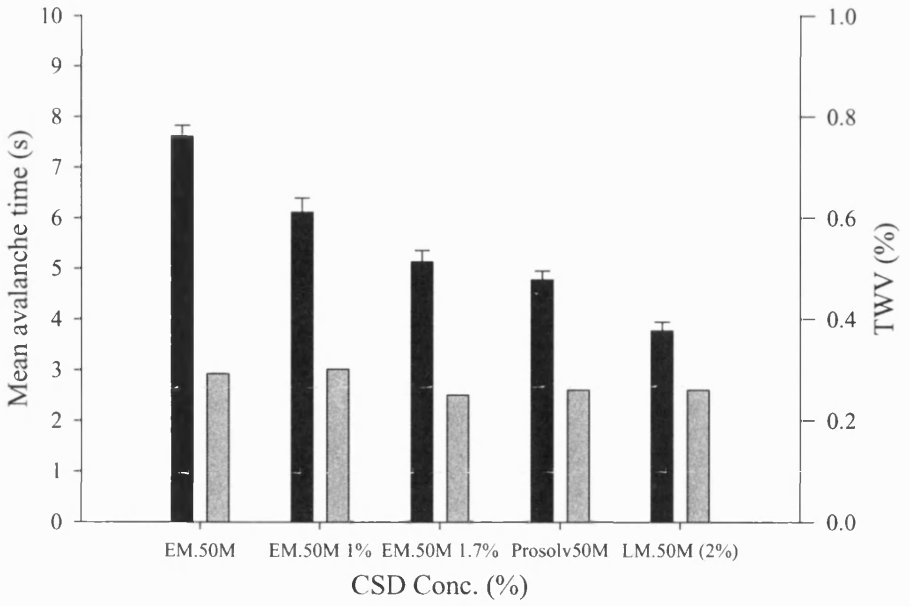



**Fig. 3.13.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 43%) for Emcocel 50M series. Mean avalanche time ▮ and tablet weight variation ▮.

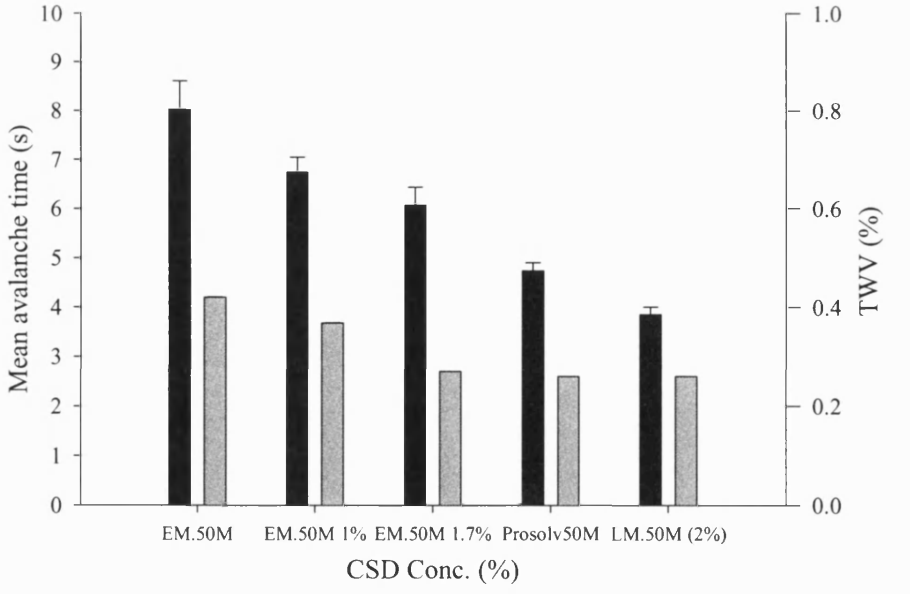



**Fig. 3.14.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 58%) for Emcocel 50M series. Mean avalanche time ▮ and tablet weight variation ▮.

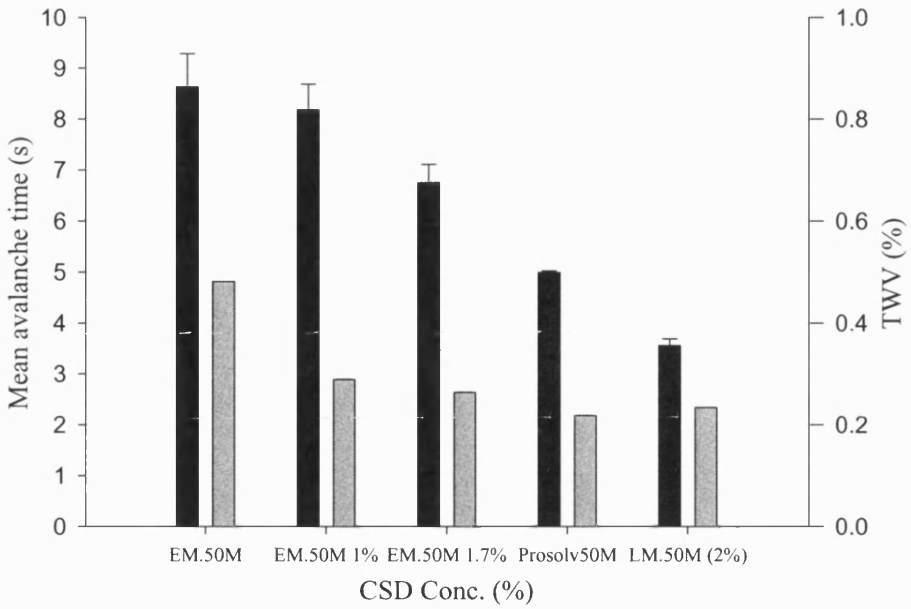



**Fig. 3.15.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 72%) for Emcocel 50M series. Mean avalanche time ▮ and tablet weight variation ▮.

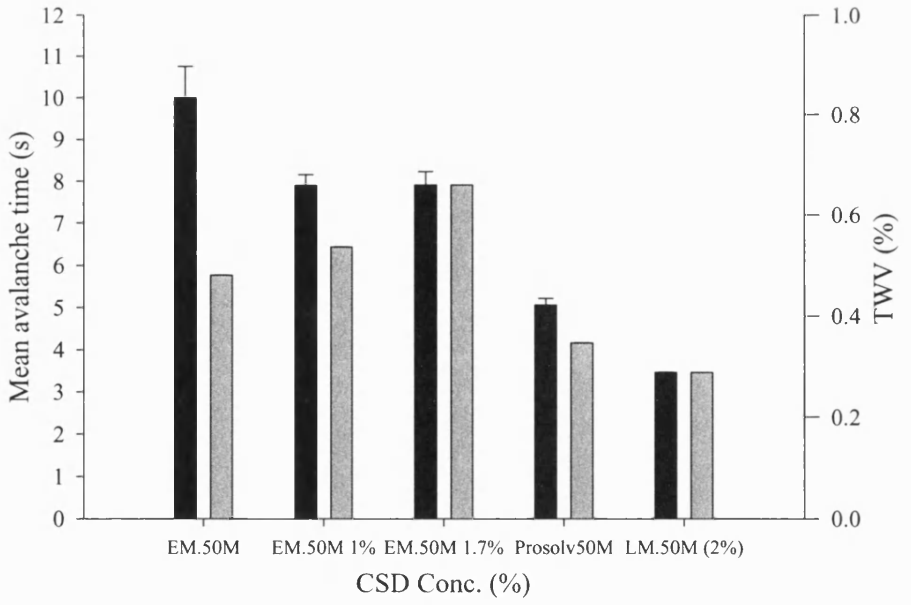



**Fig. 3.16.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 93%) for Emcocel 50M series. Mean avalanche time ▮ and tablet weight variation ▮.

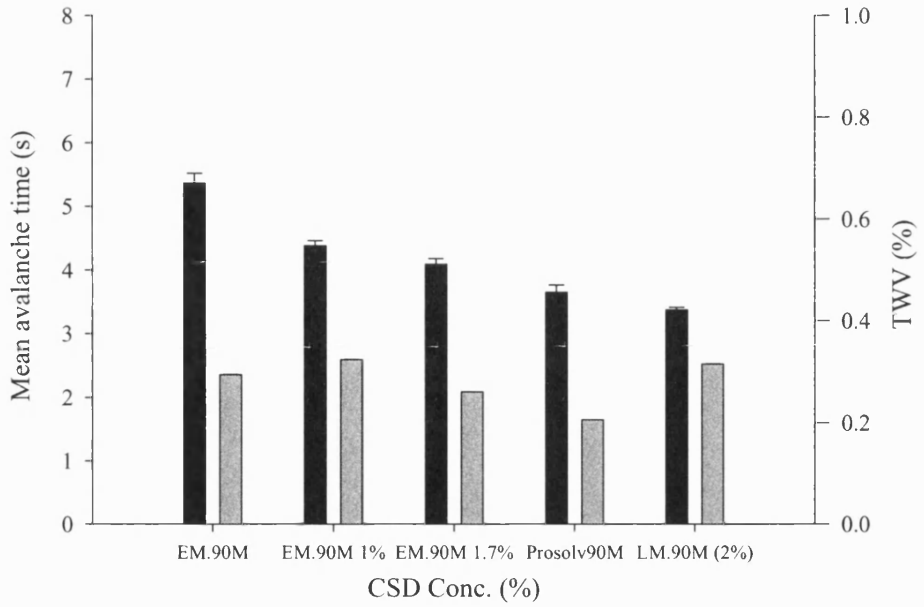



**Fig. 3.17.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 8%) for Emcocel 90M series. Mean avalanche time ▮ and tablet weight variation ▮.

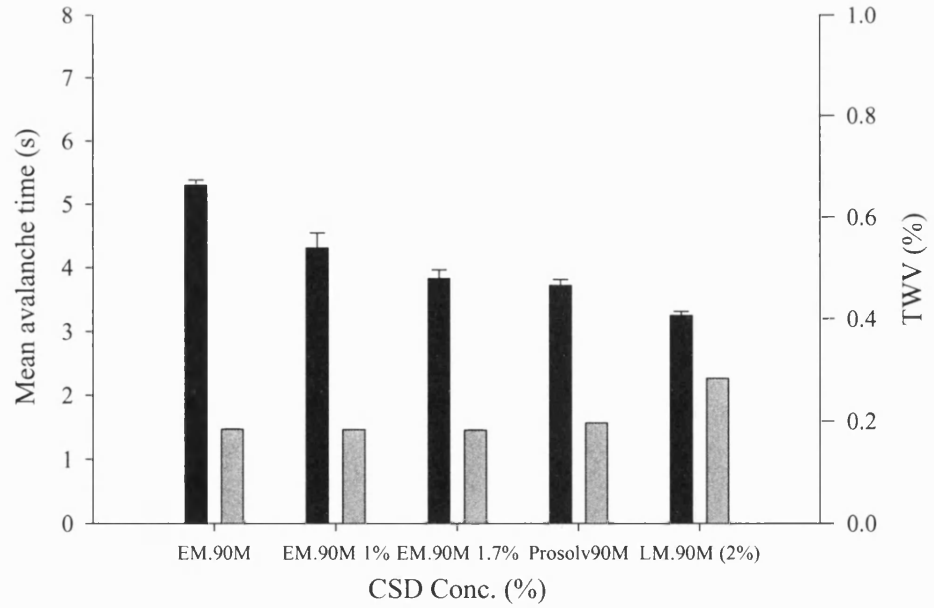



**Fig. 3.18.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 28%) for Emcocel 90M series. Mean avalanche time ▮ and tablet weight variation ▮.

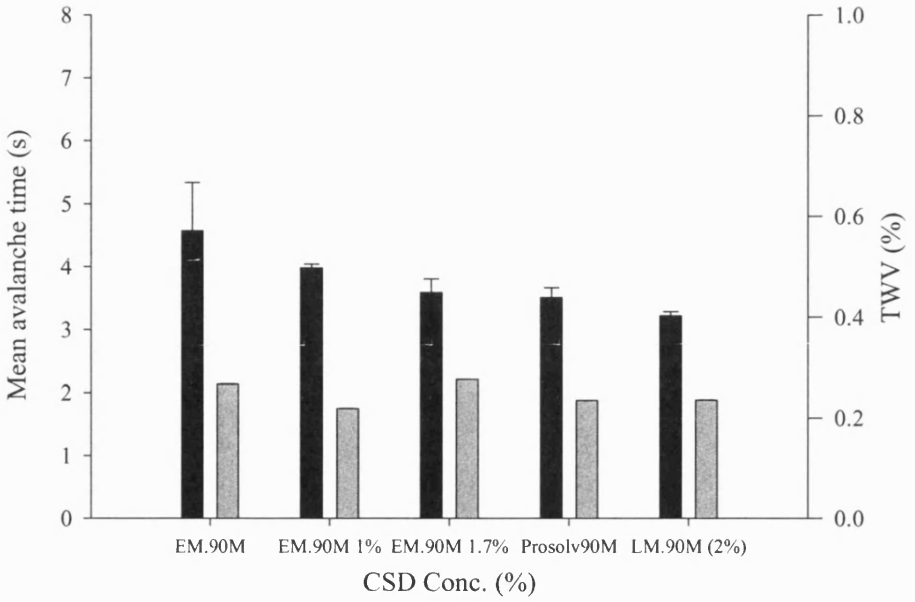



**Fig. 3.19.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 43%) for Emcocel 90M series. Mean avalanche time ▮ and tablet weight variation ▮.

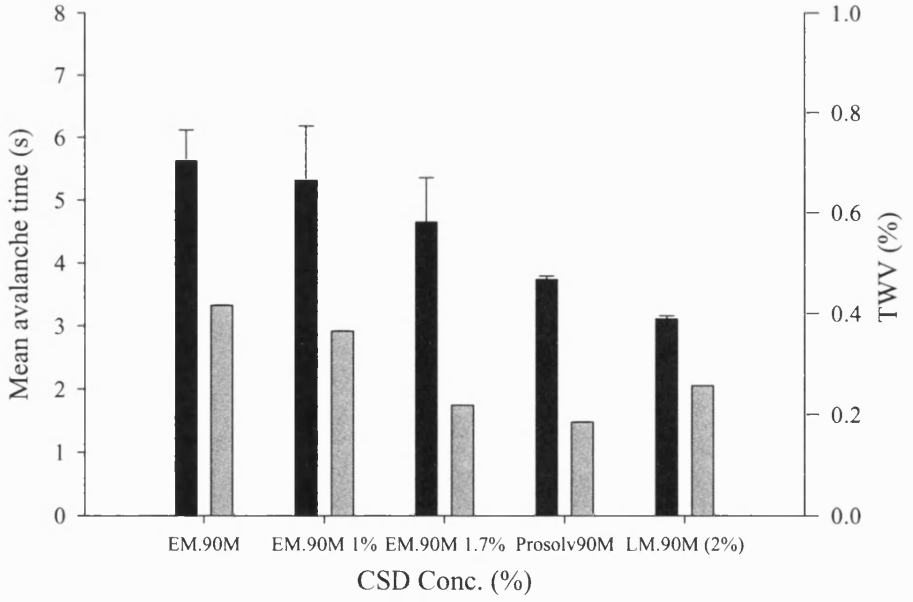



**Fig. 3.20.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 58%) for Emcocel 90M series. Mean avalanche time ▮ and tablet weight variation ▮.

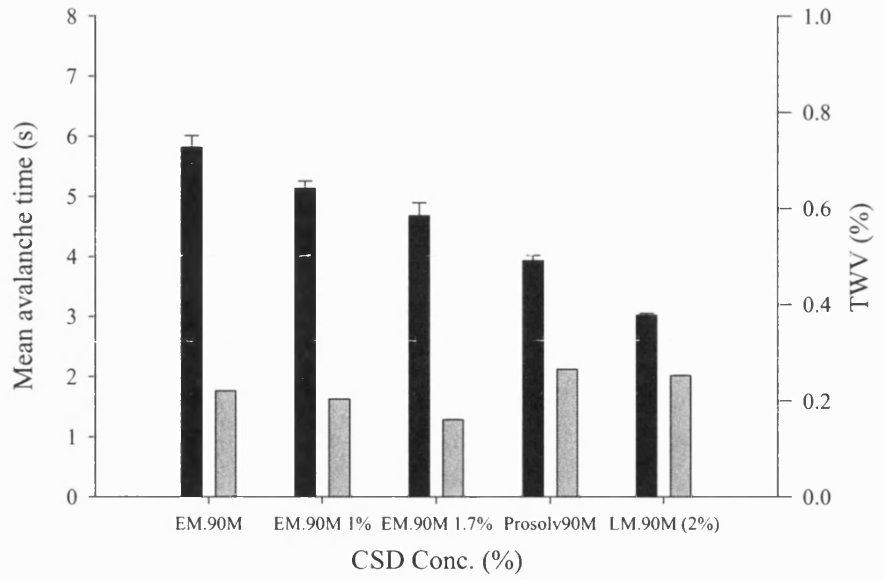



**Fig. 3.21.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 72%) for Emcocel 90M series. Mean avalanche time ▮ and tablet weight variation ▮.

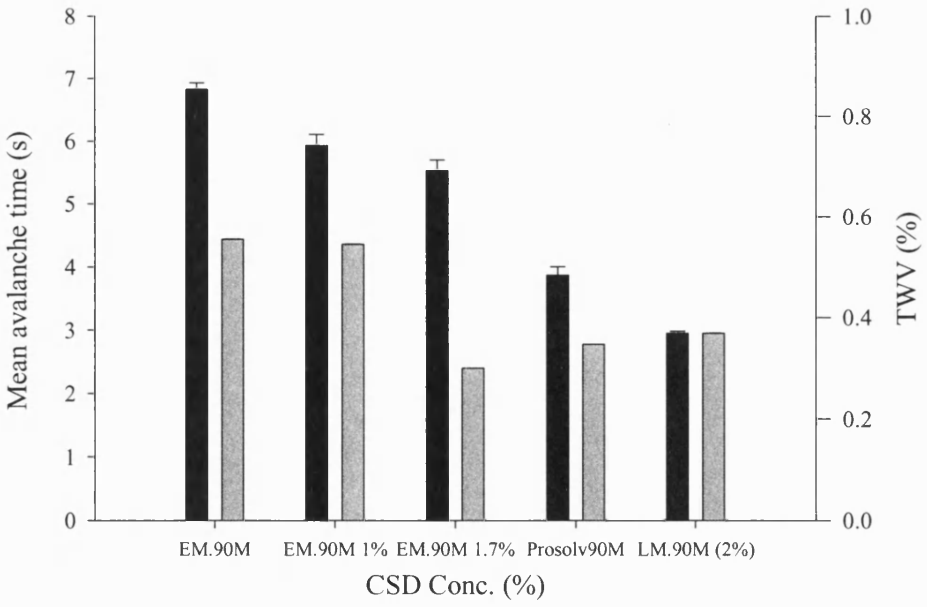



**Fig. 3.22.** The effect of CSD concentrations on the mean avalanche time and tablet weight variation at (RH = 93%) for Emcocel 90M series. Mean avalanche time ▮ and tablet weight variation ▮.

### 3.4.6. The effect of Relative Humidity on the flow Properties of Emcocel 50M/90M

Figure 3.23 shows the effect of different RHs on mean avalanche time (MAT) for Emcocel 50M and Emcocel 90M. The figure also shows the effect of RHs on tablet weight variation (TWV) of tablets prepared using the same excipients. An increase of RH from 28% to 43% resulted in a significant ($P<0.05$) decrease in (MAT), which indicates a significant improvement in powder flow. This may be due to the decrease of the effect of electrostatic charges as mentioned in section (3. 4. 3). This is examined in chapter 4. However, an increase in RHs above 43% results in a significant increase in MAT such indicating poor flow. The effect of moisture bonds and capillary forces on interparticulate interactions is expected to increase at elevated RHs, which causes such adverse effect on powder flow. This is true for both Emcocel 50M and Emcocel 90M. However, superior flow was exhibited due to the difference in particle size with Emcocel 90M than Emcocel 50M at all RHs tested. The effect of RH on tablet weight variation (TWV) is similar to that described for MAT. At elevated RHs above 43% TWV (RSD) increased as was shown for MAT for the two excipients (Emcocel 50M and Emcocel 90M). The difference between Emcocel 50M and Emcocel 90M is more evident using MAT as the parameter to describe powder flow. The difference is not significant between the weight variation of tablets prepared using the two excipients. This proves the advantage of using MAT as an in-process control to better evaluate powder flow than using only TWV as an indirect method to assess powder flow. Although this may mean that MAT produces 'false-positives', where differences in a lab technique may not transfer to the more relevant properties of tablet weight variation and capsule variation, it may be very useful in making estimates of possible flow contributions to problems. It should also be noted that the tablet machine

used here (Manesty F3) runs at a considerably slower rate (c3600 tablets per hour) and uses a different compaction technique (single station) from commercial tableting machines (which run at speeds up to 300,000 to 500,000 units per hour on a rotary technique). It may be that under such circumstances the 'false-positives' noted here are reflected in the observed results.

The effect of RH on MAT and TWV were also studied for binary powder mixes containing Emcocel 50M or Emcocel 90M and CS incorporated at different concentrations. Figures from 3.24-3.27 show the effect of RH on MAT and TWV for binary powder mixes containing both grades of Emcocel co-processed separately with CSD at 1%, 1.7% and 2%, respectively. For powder mixes containing CSD co-processed at 1% and 1.7% the increase in RH resulted in a significant increase in MAT and TWV. However, there were no significant effect on MAT and TWV of binary mixes containing 2% CS (Prosolv50M and Prosolv90M) following an increase in RH. The CS enhances flowability by coating the host particles (Emcocel 50M or Emcocel 90M) and smoothing out irregularities in their shape and reducing the frictional and adhesive forces that operate between them and forming a continuous film. Such a film is expected to be more evident at higher CS concentrations (2% for example). Studies carried out by Edge et al. (1999) using SEM, energy dispersive X-ray (EDX) and wavelength dispersive X-ray detector (WDX) suggested that colloidal silica is primarily located in the surfaces of Prosolv (50M or 90M) particles. However, in some cases colloidal silica is also detected in the internal regions of Prosolv particles. Their results suggested that silicification of MCC (Emcocel 50M or Emcocel 90M) modifies the microscopic surface characteristics of MCC.

The lab mix was prepared by de-agglomeration of CS followed by mixing the glidant with Emcocel 50M or Emcocel 90M. It was shown by Ahmed, 1989, using EDX together with dot mapping that a silicon (from CS) exists at the surface of the host particles

(sucrose-based excipient) following blending with CS. In the present work the presence of the CS film at the surface of the microcrystalline cellulose particles of the lab mix may be responsible for improving powder flow (decrease in MAT) irrespective of the increase in RH.

Colloidal silica has the ability, due to its hydrophilicity and high surface area, to disperse water, reducing the pooling of the liquid (preventing liquid bridging). This may explain the beneficial effects on flow and sensitivity to relative humidity seen during these experiments. The relative difference between lab mixes and commercial Prosolv grades with the same apparent colloidal silica content is not as easy to explain. It is known that in Prosolv the particles of colloidal silica are distributed evenly over the surface of the MCC particle (Edge et al., 1999), whereas lab mixed grades contain agglomerates of silica, this is illustrated in the SEM micrographs of dried mixed 50M and 90M with 2%w/w in chapter 2 (figures 2.7,2.8 and 2.9). It may be that these agglomerates are more able to disperse charge and water (and act as 'ball-bearings' in the blend) and this confers a flow benefit. However, it is also possible that in Prosolv some of the surface area due to it being bonded to the MCC particle (unpublished data) is unavailable for charge dispersion and water spreading. The surface area data in chapter 2 may bear this out.

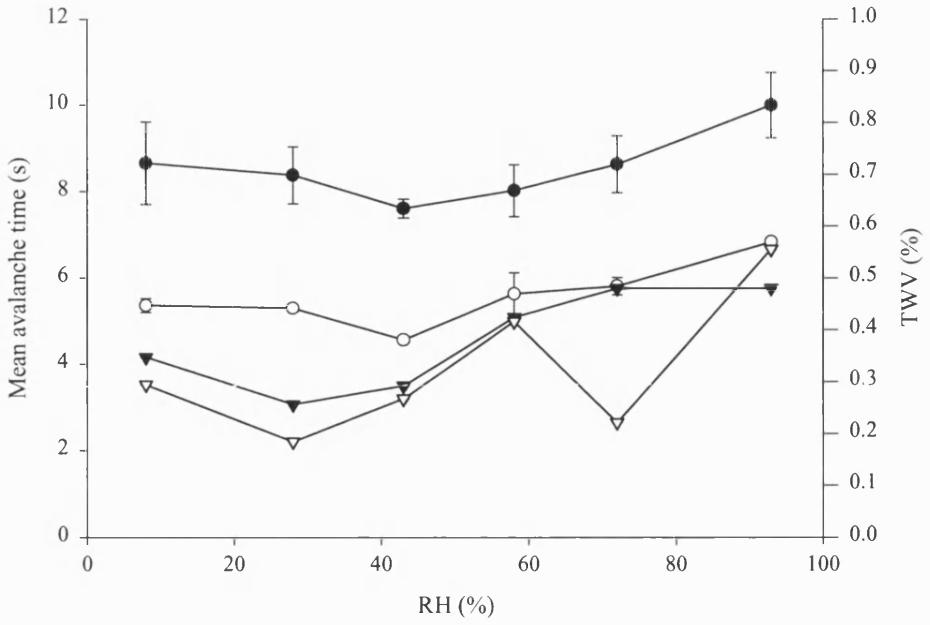



**Fig. 3.23.** Effect of different RH on mean avalanche time and tablet weight variation for Emcocel 50M. Mean avalanche time (s) (●) and tablet weight variation (▼) and for Emcocel 90M. Mean avalanche time (s) (○) and tablet weight variation (▽).

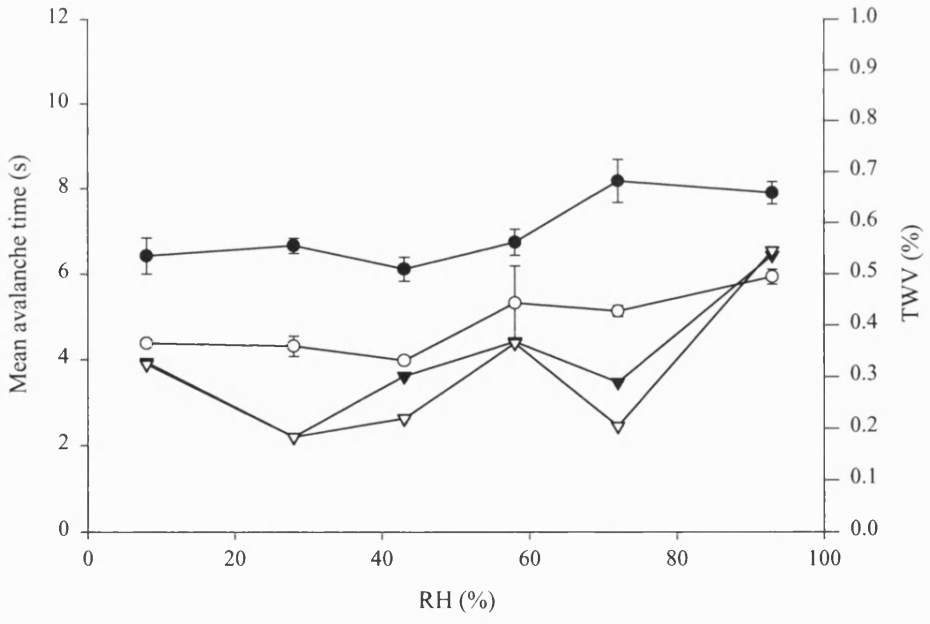



**Fig. 3.24.** Effect of different RH on mean avalanche time and tablet weight variation for Emcocel 50M 1% (CSD). Mean avalanche time (s) (●) and tablet weight variation (▼) and for Emcocel 90M 1%. Mean avalanche time (s) (○) and tablet weight variation (▽).

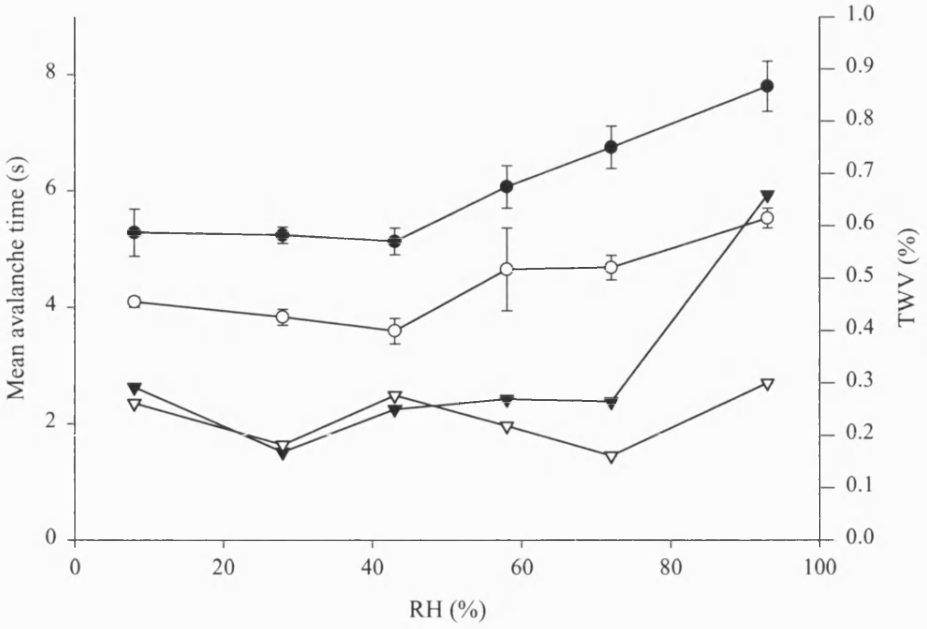



**Fig. 3.25.** Effect of different RH on mean avalanche time and tablet weight variation for Emcocel 50M 1.7% (CSD). Mean avalanche time (s) (●) and tablet weight variation (▼) and for Emcocel 90M 1.7%. Mean avalanche time (s) (○) and tablet weight variation (▽).

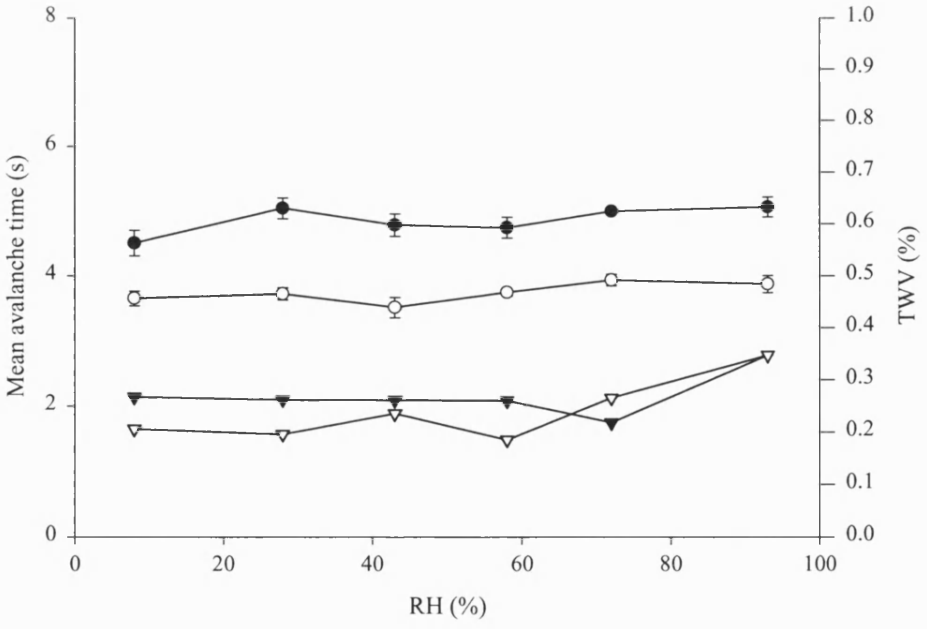



**Fig. 3.26.** Effect of different RH on mean avalanche time and tablet weight variation for Prosolv50M. Mean avalanche time (s) (●) and tablet weight variation (▼) and for Prosolv90M. Mean avalanche time (s) (○) and tablet weight variation (▽).

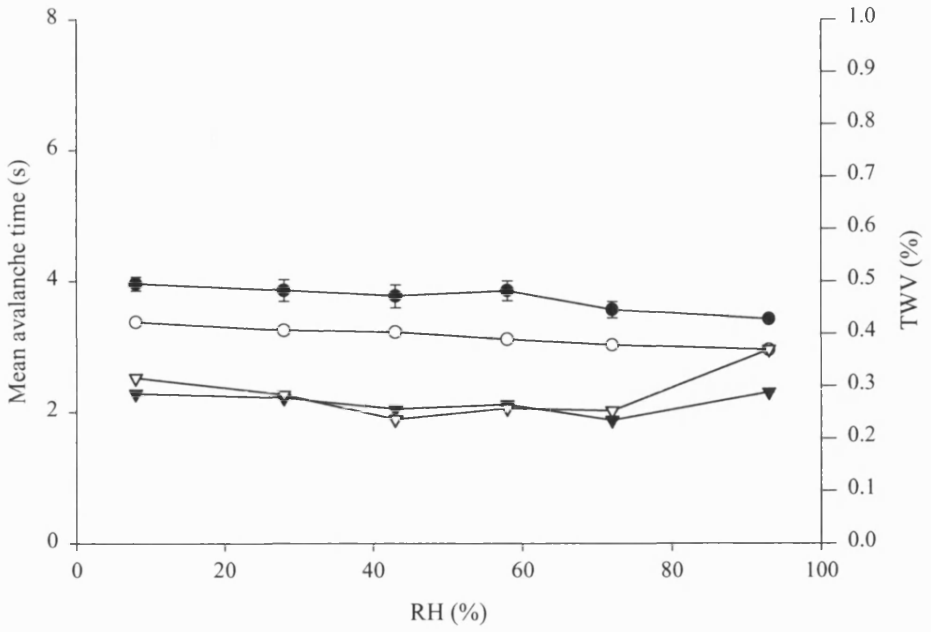



**Fig. 3.27.** Effect of different RH on mean avalanche time and tablet weight variation for lab mix 50M (2%w/w) (CSD). Mean avalanche time (s) (●) and tablet weight variation (▼)and for lab mix 90M. Mean avalanche time (s) (○) and tablet weight variation (▽).

## *3.5. Discussion*

The results contained in this chapter demonstrate that the Aero-Flow can be a useful and sensitive method of measuring the dynamic flow properties of powder. However careful attention should be paid to standardising the following properties:

1) Use of representative samples of powders;
2) 'Conditioning' of powders in constant relative humidities;
3) Use of a standard volume of powder, preferably one which minimises the possible effects of wall adhesion (i.e. a sufficiently large amount so that such losses do not unduly influence the level of tumbling powder);
4) The electrostatic characteristics of the disc (this should be carried out by drying the perspex disc carefully and using an anti-static spray to minimise wall adhesion).

Under these circumstances the instrument gave results which might have been expected for the materials initially tested. Although, as outlined above, this should not be taken as an absolute validation it could be seen as helpful in gaining confidence in the technique.

It is clear that the instrument gives different results from other measurements of flow. This is very common in flow measurements. It remains to be seen under what conditions that the discriminatory properties of the Aero-Flow are more relevant than other techniques. Increasing use of the apparatus by other groups may further help elucidate these benefits.

The effect of humidity on the results obtained emphasises, once again, the importance of the control of this parameter in pharmaceutical processing.

The beneficial flow properties of SMCC (Prosolv) grades of microcrystalline celluloses are demonstrated unequivocally, both in terms of their overall improved flow properties and resistance to changes in humidity.

# Chapter 4

# Electrostatic Charge Interaction in Microcrystalline Cellulose

## *4.1 Introduction*

Electrostatics influence a large number of pharmaceutical processes and their operation, from the flow properties of mixes to the (very real) explosion risk when using fine powders in fluid bed driers. Unit operations such as mixing, milling, sizing, and tablet compression all induce static electrification. All these operations lead to the overall charge development on granules and finished tablets, which can cause difficulties in the efficient operation of processing equipment. For these reasons it can be instructive to have some understanding (however incomplete it may be) of the electrostatic properties of powders.

Electrostatic charge measurement on pharmaceutical powders have been extensively studied using a Faraday well connected to an electrometer (Staniforth, 1980, 1982; Lord, 1993; Ahmed, 1989; Kassem, 1990; and Reis 1984).

In the absence of an externally applied electrical field, particles which come into contact with other particles or surfaces can obtain a charge which is retained when the surfaces separate. Production of an electrostatic charge by contact or frictional interaction of moving surfaces is referred to here as triboelectrification.

This chapter shows the effect of different relative humidities on the electrostatic charge of powder and the effect of different chutes on the electrostatic charge. Furthermore a correlation between the mean avalanche time and electrostatic charge at different relative humidities will be found out. It is understood that the observations made may not be used

to indicate absolute levels of charge but may have some value for comparison purposes between different humidities and materials.

## *4.2. Material and Method*

### 4.2.1. Apparatus

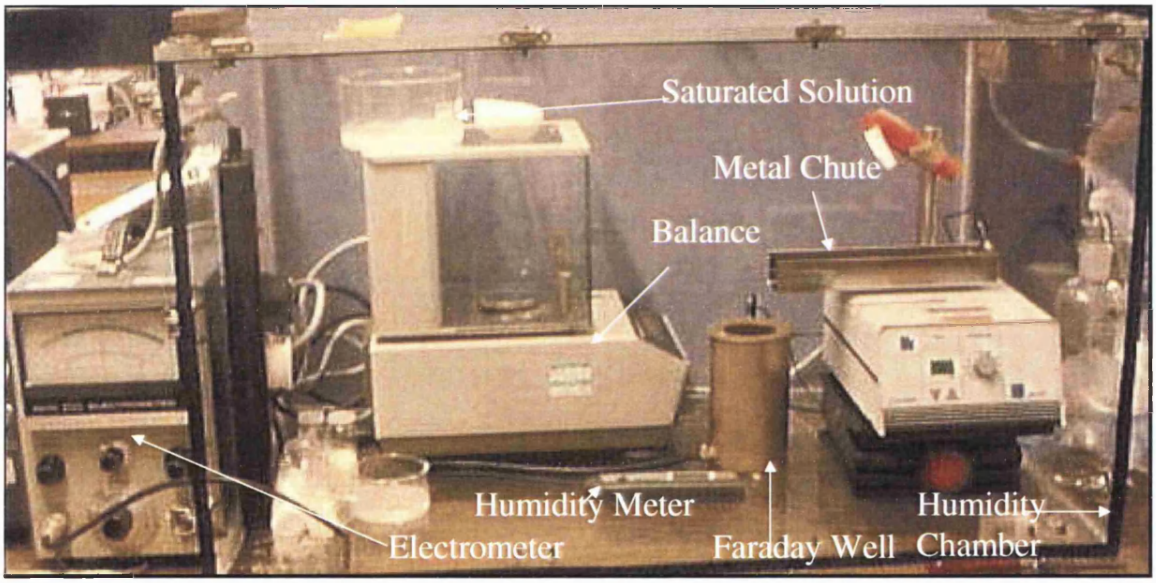



**Figure 4.1**. Photograph of Faraday well using metal chute in humidity chamber.

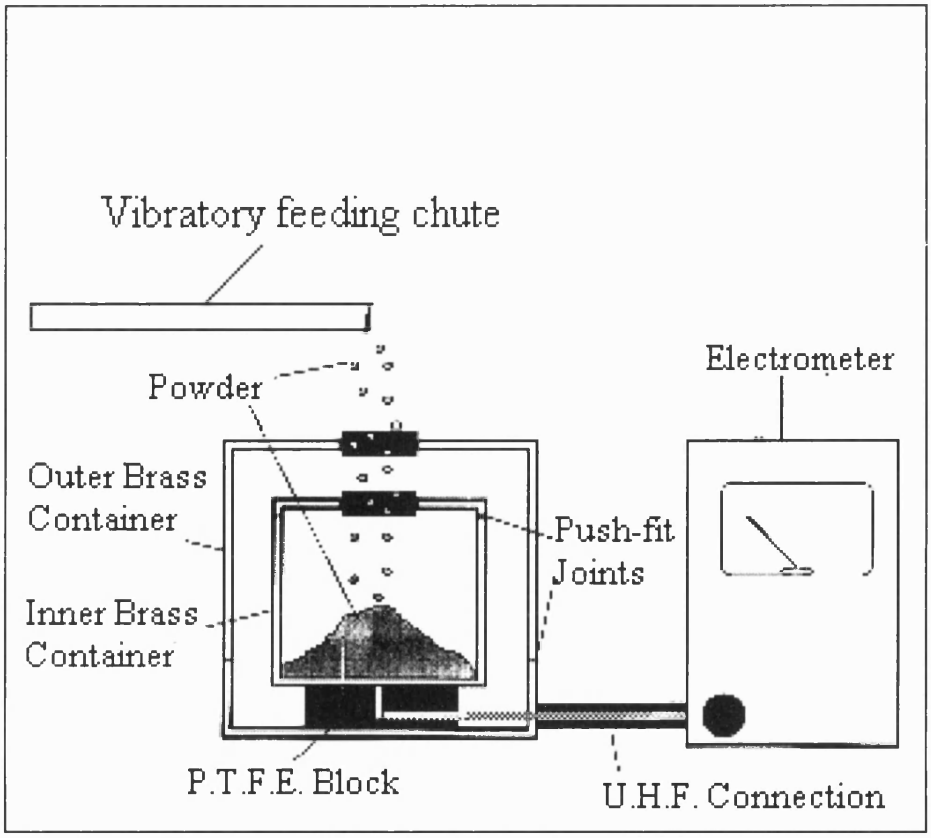



**Figure 4.2**. Schematic diagram of the Faraday well.

Instrumentation for electrostatic charge measurement has been comprehensively reviewed by (Secker and Chubb, 1984). The standard method for the measurement of the electrostatic charge is the use of a Faraday pail or well (fig.4.2), coupled to a suitable monitoring circuit. The Faraday well is a conducting container, enclosed by an outer earthed well to reduce interference from nearby electrostatic fields or charges. The inner well is connected by a shielded co-axial cable to an electrometer, which measures charges by detecting the voltage built up across a known capacitance.

When a charged object is introduced into the well, an equal and opposite charge is induced on the inner walls of the well. This charge leaves behind an equal and opposite charge on the capacitor of the electrometer, which can be measured to give the charge inside the well. Results are usually presented in terms of the charge-to-mass ratio, or specific charge, q/m, whereby the charge (q) is measured on a quantity of the powder, which is then weighed (m).

The initial objective of this part of the study was to investigate the variability of electrostatic charge measurements, with the view to a more detailed understanding of the processes and variables involved, and the reduction of the inherent variability of the system, to a level where confidence in the results produced could be assured.

Humidity, together with the relative number of particle-particle and particle-surface collisions are considered to be significant parameters influencing the electrostatic behaviour of pharmaceutical materials. Control of these factors should, in theory, reduce the inherent variability associated with electrostatic charge measurement system (Staniforth, 1982; Lord, 1993).

Standardisation of both humidity and the number of particle collision, and consequently the developed frictional charge, might be facilitated through conduction of

the experiments within a controlled environment, using a vibrating powder chute, where the vibration frequency can be easily controlled (Peart, 1996). Preliminary studies were, therefore, conducted to investigate the influence of particle–particle and particle-surface collisions.

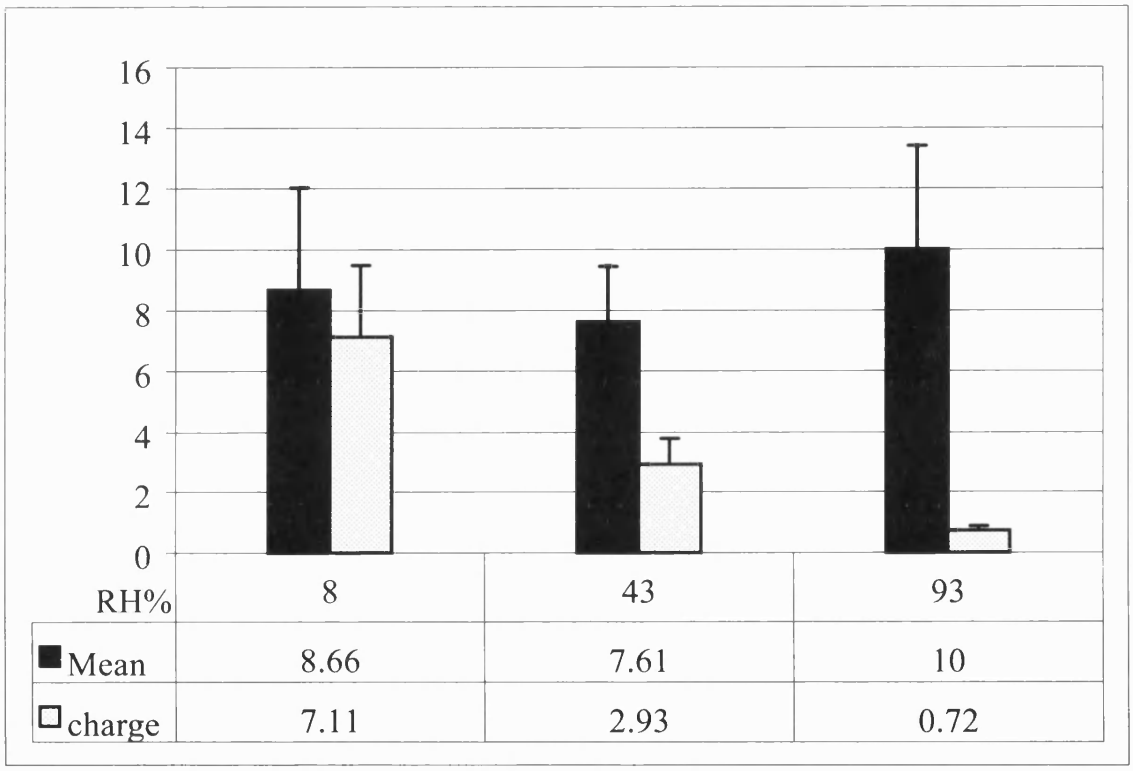
It should be noted that the reproducibility of this system has been reported to be wholly unsatisfactory with large variations reported in the magnitude of the charge. Staniforth and Ress, 1982c recorded variations of up to 50% in some determinations. (Lord, 1993) noted that although lactose poured from glass surface produced a mean electropositive value, three of the five determinations were electronegative.

### 4.2.2. Method

Electrostatic measurements were carried out as described in chapter 2 (Characterisation of materials, 2.2.4).

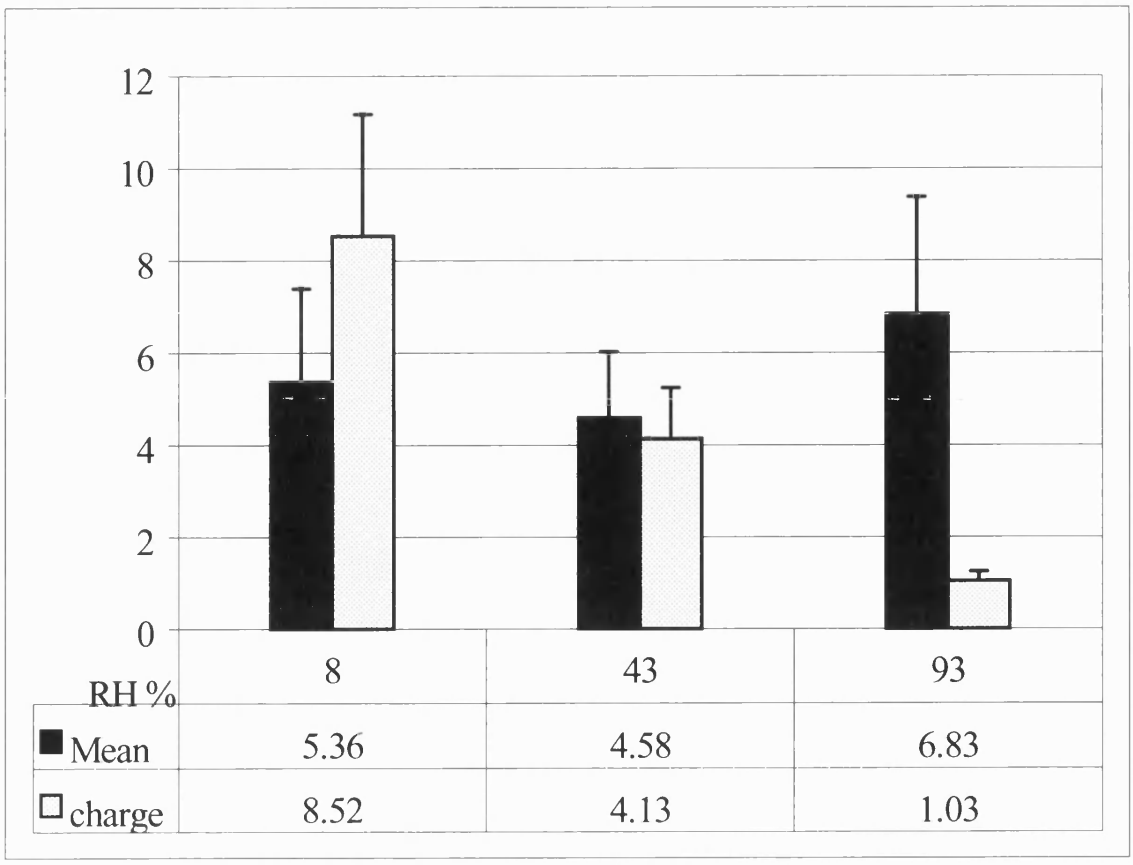
## *4.3. Results and Discussion*

### 4.3.1 Effect of Relative Humidity on Mean Specific Charge and Powder Flow of Different Powders




| RH% | 8 | 43 | 93 |
|---|---|---|---|
| Mean | 8.66 | 7.61 | 10 |
| charge | 7.11 | 2.93 | 0.72 |

**Figure 4.3**. Effect of relative humidity on mean avalanche time (s) and mean specific charge ($C.g^{-1}*10^{-9}$) for Emcocel 50M on treated plastic chute.




| RH % | 8 | 43 | 93 |
|---|---|---|---|
| ■ Mean | 5.36 | 4.58 | 6.83 |
| □ charge | 8.52 | 4.13 | 1.03 |

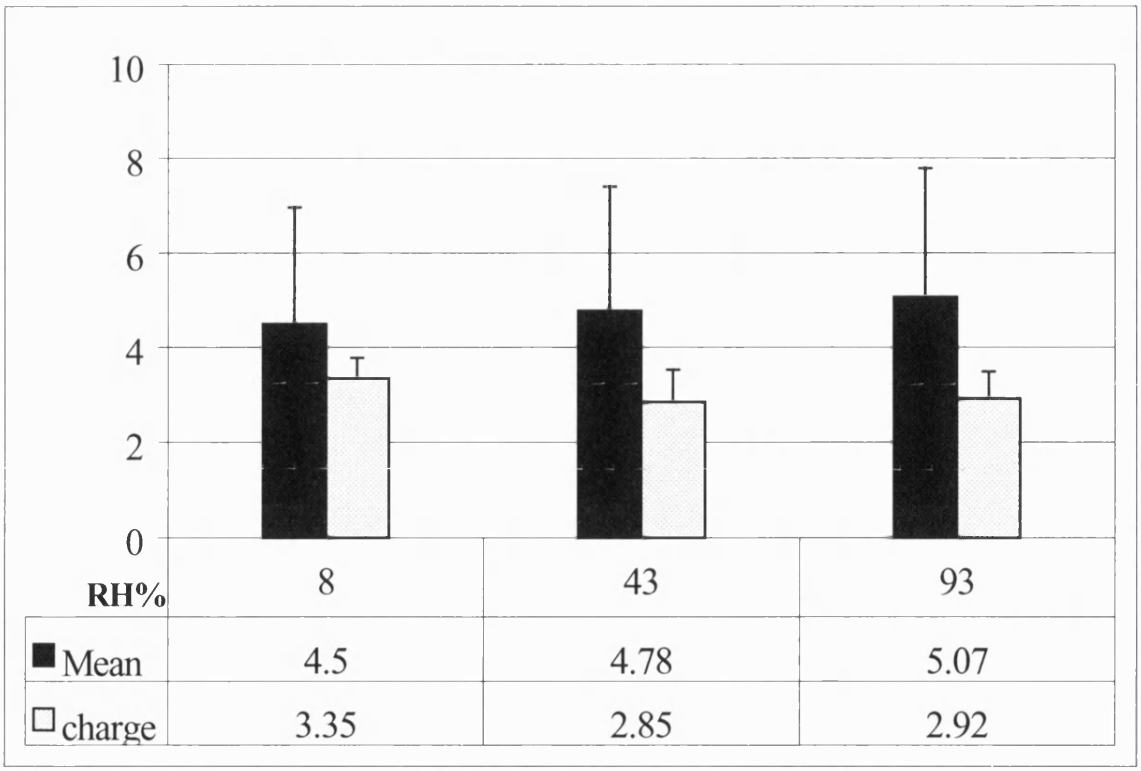
**Figure 4.4.** Effect of relative humidity on mean avalanche time (s) and mean specific charge ($C.g^{-1}*10^{-9}$) for Emcocel 90M on treated plastic chute.

Figures 4.3. and 4.4. show the effect of relative humidity on the mean specific charge and flow (MAT) for Emcocel 50M and Emcocel 90M, respectively. The two figures clearly illustrate that the increase relative humidity from 8% to 93% resulted in a significant decrease in the mean specific charge determined following flow on a treated plastic chute. For Emcocel 50M and at 8% RH where the electrical surface charge was high (7.11 $C.g^{-1}*10^{-9}$) powder flow was poor (MAT = 8.66 (s)). At low RHs the electrostatic charge interactions predominate which intensify interparticle forces and particle adhesion leading to the poor flow (higher MAT). The increase in RH from 8% to

43% results in a decrease in electrostatic charge (from 7.11 $C.g^{-1}*10^{-9}$ to 2.93 $C.g^{-1}*10^{-9}$), which was matched by a decrease in MAT (from 8.66 to 7.61 s).

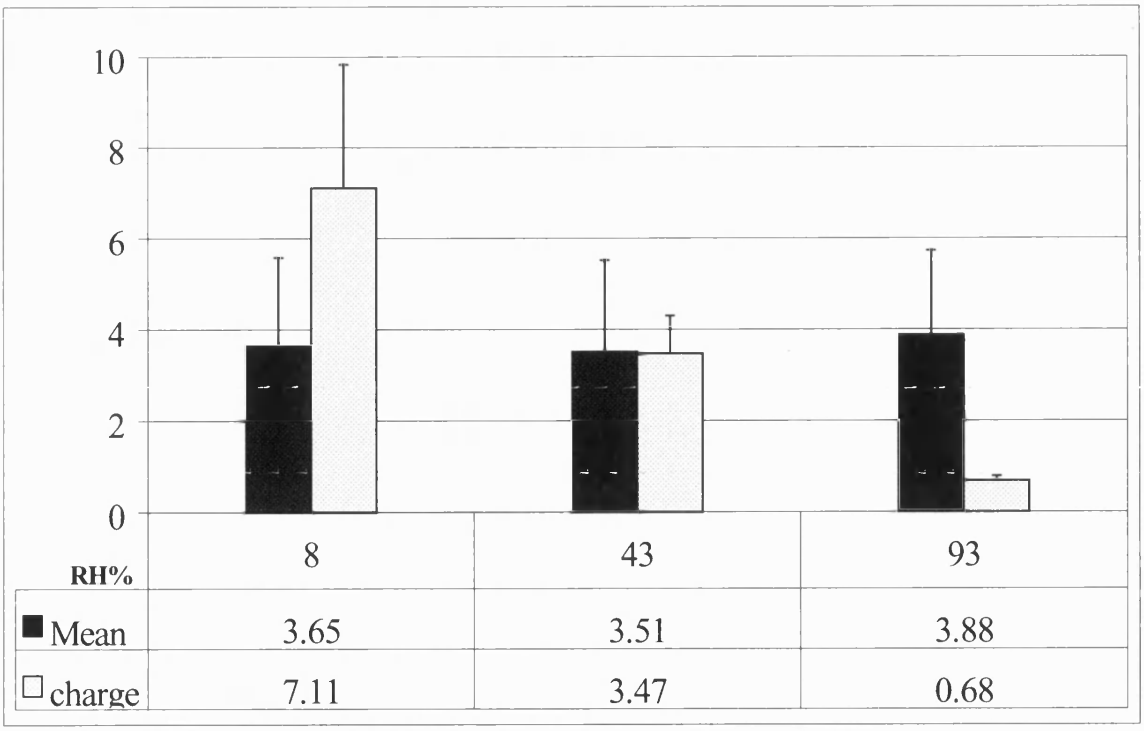
Further increase in relative humidity to 93% results in a significant decrease in electrostatic charge (down to 0.72 $C.g^{-1}*10^{-9}$), however such decrease in surface electrical charge was not matched by a decrease in MAT or improvement in powder flow. At such high relative humidity the effect of electrical charge on interparticulate forces is diminished while the effect of moisture and capillary forces predominate leading to such adverse effect on powder flow.

The attractive capillary force is the result of the formation of a liquid bridge at the gap between particles making actual contact. Emcocel 90M performed in a manner similar to Emcocel 50M. Higher MAT values were obtained at low and high RHs with the optimal flow at 43%. Emcocel 90M demonstrated superior flow than Emcocel 50M at all relative humidities investigated. Higher specific charges were obtained with Emcocel 90M than those obtained with Emcocel 50M at all relative humidities tested. The fact that lower charges were obtained with Emcocel 50M than with Emcocel 90M is due to particle size difference. It was shown by Bennet et al., (1999) that the magnitude of charge on the lactose mixes decreased with increased fine particle content, whereas the variation of charge and powder adhesion to the stainless steel cyclones surface increased with increase in fine particle content.




| RH% | 8 | 43 | 93 |
|---|---|---|---|
| Mean | 4.5 | 4.78 | 5.07 |
| charge | 3.35 | 2.85 | 2.92 |

**Figure 4.5**. Effect of relative humidity on mean avalanche time (s) and mean specific charge ($C.g^{-1}*10^{-9}$) for Prosolv50M on treated plastic chute.




| RH% | 8 | 43 | 93 |
|---|---|---|---|
| Mean | 3.65 | 3.51 | 3.88 |
| charge | 7.11 | 3.47 | 0.68 |

**Figure 4.6.** Effect of relative humidity on mean avalanche time (s) and mean specific charge ($C.g^{-1}*10^{-9}$) for Prosolv90M on treated plastic chute.

Figures 4.5. and 4.6. show the effect of relative humidity on the mean specific charge and flow (MAT) for Prosolv50M and Prosolv90M, respectively. The increase in relative humidity did not have a significant effect on MAT of Prosolv50M. At all relative humidities Prosolv50M, which is a co-processed Emcocel 50M with 2% CSD, exhibited lower MAT (or superior flow) than Emcocel 50M and comparable flow properties to Emcocel 90M at 8% and 43% RHs. At 93% RH Prosolv50M demonstrated better flow than Emcocel 90M (MAT equals 5.07 s and 6.83 s, respectively.). Prosolv90M demonstrated superior flow than all mentioned powders (Emcocel 50M, Emcocel 90M and Prosolv50M) at all tested relative humidities. Unlike, Prosolv50M the increase in relative

humidity results in significant decrease in magnitude of electrostatic charge 7.11 to $0.68X10^{-9}C$ when RH increased from 8% to 93%, respectively.

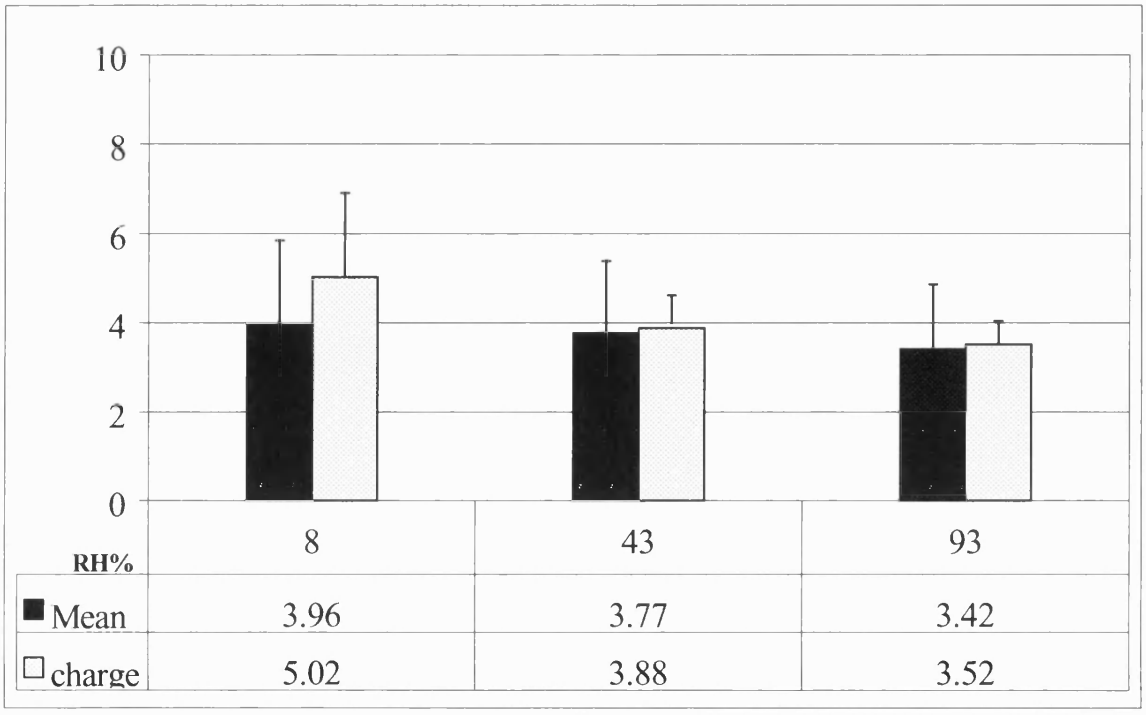



**Figure 4.7**. Effect of relative humidity on mean avalanche time (s) and mean specific charge ($C.g^{-1}*10^{-9}$) for lab mix 50M on treated plastic chute.

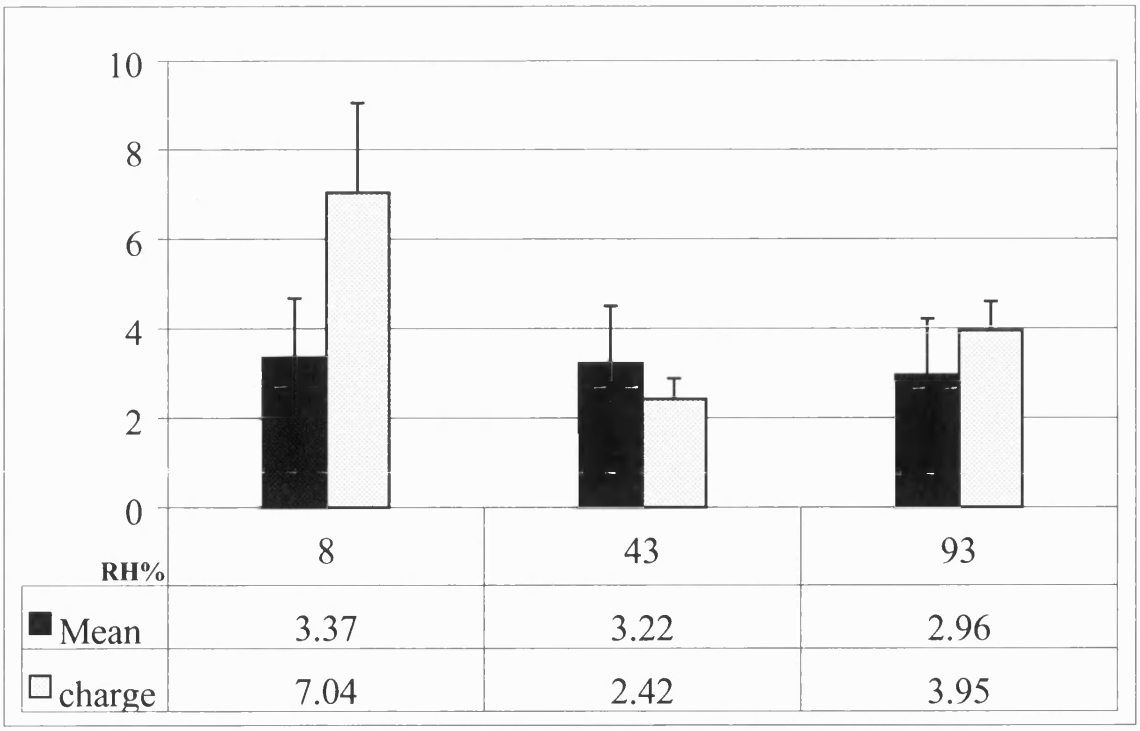



**Figure 4.8.** Effect of relative humidity on mean avalanche time (s) and mean specific charge ($C.g^{-1}*10^{-9}$) for lab mix 90M on treated plastic chute.

Figures 4.7. and 4.8. show the effect of RH on mean specific charge and flow of lab mix 50M and lab mix 90M, respectively. lab mix 50M demonstrated comparable flow properties to Prosolv50M. Specific electrical charge decreased from 5.03 $C.g^{-1}*10^{-9}$ to 3.88 $C.g^{-1}*10^{-9}$ when relative humidity increased from 8% to 43%. Further increase in relative humidity did not cause a significant change in electrostatic charge. However, for lab mix 90M an increase in relative humidity resulted in a significant decrease in electrostatic charge especially between 8% to 43%.

### 4.3.2. Effect of RH on Reproducibility of Specific Charge Properties Following Flow of Binary Powder mixes on Different Chutes

The change in a particle's electrical properties alters its electrostatic force attraction and adhesion to surfaces. It was shown earlier that electrostatic charges might affect powder flow and other unit operations during processing including mixing. Therefore, the electrostatic force on particles near surfaces needs to be monitored and controlled. The effect of relative humidity and surface moisture on electrostatic forces was discussed earlier .To completely characterise this phenomenon the effect of relative humidity and surface moisture on reproducibility of electrostatic charges following flow of different binary powder mixes on different chutes will be discussed in this chapter.

| Sample | Emcocel 90M | Prosolv 90M | Lab mix 90M | Emcocel 50M | Prosolv 50M | Lab mix 50M |
|---|---|---|---|---|---|---|
| R.H% | RSD% | RSD% | RSD% | RSD% | RSD% | RSD% |
| 8 | 45.87 | 55.03 | 43.43 | 40.68 | 44.15 | 49.07 |
| 43 | 29.89 | 28.96 | 25.76 | 39.31 | 30.33 | 29.81 |
| 93 | -23.26 | -19.18 | -21.49 | -28.01 | -25.58 | -20.17 |

**Table 4.1** Effect of Relative Humidity on RSD of Specific Surface Charges Generated for Different Powders Following Flow on a Plastic Chute

Table 4.1 shows the effect of relative humidity on RSD of the specific charges generated for different powders following flow on a plastic chute. Following flow on a plastic chute all powders acquired electropositive charges except at 93% relative humidity

where charge reversal to electronegative was observed. Charge reversal occurs as results of particle-particle interactions rather than particle-surface friction. The effect of relative humidity on RSD is clearly demonstrated for different powders tested. The increase in relative humidity resulted in a significant decrease in RSD indicating an increase in material conductivity. Moisture adsorbed in humid environments, greatly increases the surface conductivity of dielectric particles (Tombs, 1995). The resistivity of the materials investigated decreased sharply as the moisture content was increased. Research on single particles by Tombs and Jones, 1993 illustrated the time dependence brought on by adsorbed moisture, which manifests as a relaxation in the particle's dipole moment. Using atomic force microscopy, Mizes, 1994 measured the force on a single particle in air a fixed distance above a ground plane. When an external field was applied, the force increased over time by an order of magnitude. Such increase was attributed to surface conductivity.

The effect of RH on RSD of surface charges is similar following flow of the same powders on a treated plastic chute (with antistatic) and a metal chute (Tables 4.2 and 4.3. respectively). There were no significant differences in RSD of the generated electrostatic charges for different powders investigated. The determining factor affecting reproducibility of the electrostatic charges is the type of the chute together with the relative humidity regardless of the powder mixes investigated.

For the majority of materials tested the calculated RSD values obtained from metal determinations (<26%) were smaller than those obtained with plastic and treated plastic (55% and 38%, respectively). The treated plastic chute was sprayed with an antistatic agent described earlier in chapter 3. The antistatic agent was used to reduce the interference from the remaining charges on a plastic chute and counteracting the effects of charging in general. The use of the antistatic agent not only improved reproducibility of electrostatic charges on the plastic chute but also improved powder flow over the chute.

Electrostatic charge arises as the separation of positive and negative charges at the interface between two dissimilar surfaces. When powder particles move along the vibrating chute, an equal and opposite charge is left upon the chute. The metal chute is a conductor, and as such, the developed charge can redistribute itself, eventually to earth. At the beginning of measurement the chute will be in equilibrium with earth. On the other hand, the plastic chute is an insulator with high resensitivity, and the developed charge will remain "locked" on the surface, as the electrons are not able to move freely. Such charge is expected to interfere with the subsequent determinations. Therefore, the metal illustrated more reproducible charge measurements unlike the plastic surface.

| Sample | Emcocel 90M | Prosolv 90M | Lab mix 90M | Emcocel 50M | Prosolv 50M | Lab mix 50M |
|---|---|---|---|---|---|---|
| R.H% | RSD% | RSD% | RSD% | RSD% | RSD% | RSD% |
| 8 | 31.24 | 38.2 | 28.74 | 29.68 | 31.03 | 37.65 |
| 43 | 26.73 | 23.98 | 19.07 | 29.01 | 27.31 | 23.84 |
| 93 | 20.39 | 15.88 | 16.48 | 20.1 | 19.52 | 11.83 |

**Table 4.2.** Effect of Relative humidity on RSD of Specific Surface Charges Generated for Different Powders Following Flow on a treated Plastic Chute.

| Sample | Emcocel 90M | Prosolv 90M | Lab mix 90M | Emcocel 50M | Prosolv 50M | Lab mix 50M |
|---|---|---|---|---|---|---|
| R.H% | RSD% | RSD% | RSD% | RSD% | RSD% | RSD% |
| 8 | 26.07 | 25.77 | 25.07 | 14.31 | 12.56 | 17.93 |
| 43 | 5.56 | 10.45 | 19.11 | 12.21 | 13.04 | 15.46 |
| 93 | 7.54 | 10.61 | 10.98 | 9.12 | 9.46 | 11.62 |

**Table 4.3.** Effect of Relative humidity on RSD of Specific Surface Charges Generated for Different Powders Following Flow on a Metal Chute.

## *4.4. Discussion*

### 4.4.1. Effect of humidity on charge transfer

The use of electrostatic techniques demonstrated many of the problems inherent in the use of such methods, most obviously the high variability of results, even when significant attempts are made to reduce the level of such problems. The technique was able to capture the (significant) changes in charge development as the storage humidities of powders increased.

In presence of high humidity, the polar substance has multimolecular water sorption layer and have a relatively frequent exchange of the water molecules of the particle surface with those of the atmosphere thus, the charge can leave the particles (Fuiher, 1996)

As a result the total charge of the particles will be relatively low compared with materials without polar group in the surface and no water sorption layer.

If two different powdered materials are mixed, the particles of the two materials attract each other because of their opposite polarities thus, an increase in the bulk density occurs and the flowability of the powders decreases. (Fuiher, 1996)

On the other hand, powders charged with a uniform polarity have low bulk densities and good flowability due to the interparticular repulsion forces.

In addition to the triboelectrostatic charges, particles possess a permanent electrostatic charge depending upon the surface structure of the powder (Musters, 1977). This charge cannot be transferred. It can only be suppressed by oppositely charged materials. This permanent charge on the surface depends upon the ions in case of salts and/or presence of functional polar groups in the crystalline material.

However the methods used were unable to give a coherent picture of the differences between different materials, when measured under the conditions described. In particular the differences between Prosolv materials and lab mix materials, with the same colloidal silica content but different distributions, could not be readily explained by these techniques. At this stage it is not clear whether this is because such differences do not exist or because of the limitations of the electrostatic methods described here.

# Chapter 5:

# Powder Mixing

## *5.1. Introduction*

Powder mixing is one of the most important unit operations in the production of solid dosage forms. At this stage the likely maximum homogeneity of the solid system is generated prior to the final tableting or encapsulation. The determination of drug homogeneity is essential during both preformulation and formulation of pharmaceutical solid dosage forms. The benefits of solid dosage forms in terms of their speed of manufacture and low variability in content uniformity (tablets have a specification of ±5% of stated content and frequently achieve far better homogeneity) is dependent on good mixing characteristics.

The work described in this chapter is an investigation on the effect of mixing time on the homogeneity and content uniformity of a drug incorporated at a low dose. The work attempts to discover whether the improved flow properties of the novel microcrystalline cellulose grades lead to improved mixing characteristics, as might be expected. The effect of mixing time on the specific electrostatic charges was also investigated in this chapter. This chapter also investigates the effect of different excipients properties (namely particle size distribution) on drug homogeneity in binary, ternary and quaternary powder mixes, and whether the new grades of material can provide resistance to the deleterious effects of magnesium stearate on blends.

### 5.1.1. Theoretical assessment of powder mixes

Johnson (1972, 1975, 1979a, 1979b) and others (Poole et al., 1964; Johnson and Cullinan, 1977; Kaufman, 1962; Samyn and Murthy, 1974), have used measurements of the coefficient of variation (CV) of random samples selected from different locations in a powder mix to assess its uniformity and homogeneity. The use of the mean as a denominator when calculating the CV has a standardizing effect on data which is useful for comparison of powder mixes having different theoretical mean drug content. The theoretical coefficient of variation of samples containing less than 1% drug was developed by Johnson in (1972):

$$CV = 100\ (\pi\rho/6G)^{1/2}.\ (\sum fd3)^{1/2} \qquad \text{Equation 5.1}$$

Where CV is the coefficient of variation of a binary mix, $\rho$ is the mean particle true density, G is the percentage by weight of one component of a mix, f is the weight fraction within a class interval, d is the adherent particle diameter. Although a broad variety of other methods for assessing powder uniformity have been reported in the literature, measurements of the coefficient of variation were considered most suited to the present study and have been used throughout this work.

## *5.2. Study of Particle Interactions in Binary, Ternary, and Quaternary Powder Mixes*

### 5.2.1. Apparatus

The TURBULA® Unit Type T2C (Manufactured by: Willy A. Bachofen AG, Maschinenfabrik, Utengasse 15/17, CH_4005 Basal/Switzerland) was used in this study by making use of a service-proved kinetic principle (reversal kinematics), the fed charge in the service container is subjected to the action of a three dimensional motion produced by a drive via the two knuckle joints. Due to the compound action of the three-dimensional motion, a continuous motion implying two alternating intermittent vortices is imparted to the mixed stock. The intensity of the mixing process can be controlled by varying speed and /or the degree of container loading.

### 5.2.2. Materials

Microcrystalline cellulose based excipients, Emcocel 50M, Emcocel 90M, Prosolv90M and Prosolv50M. Dicalcium Phosphate-based excipient, Emcompress 200 and sucrose-based excipient Lactose D30. These excipient were used as model carrier substrates. Chlorpheniramine maleate was used as a model drug, magnesium stearate, as a lubricant, and colloidal silica Aerosil 200 as a glidant and flow aid. Details of the batch numbers and suppliers are given in table 2.1.

### 5.2.3. Methods

#### *5.2.3.1 Binary Mixtures*

Adhesive binary mixtures containing different excipients with model drugs were prepared. Microcrystalline cellulose based excipients, Emcocel 50M, Emcocel 90M, Dicalcium Phosphate dihydrate based excipients, Emcompress 200, and lactose excipient LactoseD30. Each of these excipients was blended with 1% w/w chlorpheniramine maleate using a mortar and metal rod. Pre-blends were subsequently further mixed, in a Turbula blender, for 1, 5, 15, 30 and 60 minutes.

#### *5.2.3.2. Ternary Mixtures*

Ternary mixes were prepared as for binary mixes described above together with 2% colloidal silica (Aerosil 200) powder pre-mixed in a high shear mixer to break up the agglomerates. Colloidal silica 2% was mixed, separately, with 97% of Emcocel 50M, Emcocel 90M, Emcompress 200 or Lactose D30 and then blended together with 1% of chlorpheniramine meleate using a mortar and metal rod. Pre-blends were subsequently further mixed, in a Turbula blender, for 1, 5, 15, 30 and 60 minutes.

For Prosolv50M and Prosolv90M 99% of each was mixed directly with 1% chlorpheniramine maleate.

*5.2.3.3. Quaternary Mixtures*

Quaternary mixes were prepared as for ternary mixes described above together with 2% colloidal silica (Aerosil 200) powder, 1% magnesium stearate and 1% model drug chlorpheniramine maleate. Colloidal silica 2% was mixed, separately, with 96% of Emcocel 50M, Emcocel 90M, Emcompress 200 or Lactose D30. These preparations were mixed with 1% magnesium stearate then blended together with 1% chlorpheniramine maleate using a mortar and metal rod. Pre-blends were subsequently further mixed, in a Turbula blender, for 1, 5, 15, 30 and 60 minutes.

Ternary mixes of Prosolv50M and Prosolv90M were prepared by blending 98% of each with 1% magnesium stearate and 1% of chlorpheniramine maleate.

*5.2.3.4. Effect of mixing time on the electrostatic charge properties following flow on different chutes*

Binary, ternary and quaternary mixtures were prepared as described earlier and mixed, in a Turbula blender, at different periods of times (1, 5, 15, 30 and 60 minutes)(Staniforthand and Ress, 1982a). Electrostatic measurements were carried out using 0.5g of each sample. Each sample was run ten times on a vibrator chute attached to an electrometer (Keithley 610C Electrometer). Each sample was run on three different chutes; metal, plastic and treated plastic (plastic chute spread with anti-static agent). The correlation between the mixing time and the electrostatic charge mean, for each mix, was plotted. In order to reduce the influence of electrostatic effects on plastic chute, prior to testing the chute was sprayed with anti-static spray (RS Anti-static cleaner 569-284, Northants, U.K).

*5.2.3.5 Analytical Assay for Chlorpheniramine Maleate*

A spectrophotometer method was used to determine chlorpheniramine maleate content. Standard solutions of known concentrations were prepared from analytical grade chlorpheniramine maleate. 0.05 gm chlorpheniramine maleate was dissolved in 0.1M HCl to give 100 ml solution containing (0.50 mg/ml). This was used as a stock solution from which five calibration standard concentrations were prepared. Volumes of 1, 2, 3, 4 and 5ml from the stock solution were pipetted into 50ml volumetric flasks and 0.1M HCl was added to give 50ml solution containing 0.01, 0.02, 0.03, 0.04 and 0.05 mg/ml respectively. The relationship between solution concentration and absorption at 264 nm was found to be linear (r =0.9999) as shown in figure 5.1.

Binary, ternary and quaternary mixtures were prepared as described earlier and mixed, in a Turbula blender, at different periods of times (1, 5, 15, 30 and 60 minutes). For each mixing time 10 samples weighing 100 mg were prepared for binary, ternary and quaternary mixtures and then dissolved in 50 ml volumetric flask. Each mixture was analysed 10 times by using, spectrophotometer, and the absorbance at 264 nm. Concentrations were interpolated using the calibration curve and the CV% was calculated for each blend. The correlation between mixing time and the drug distribution for each mix was plotted.

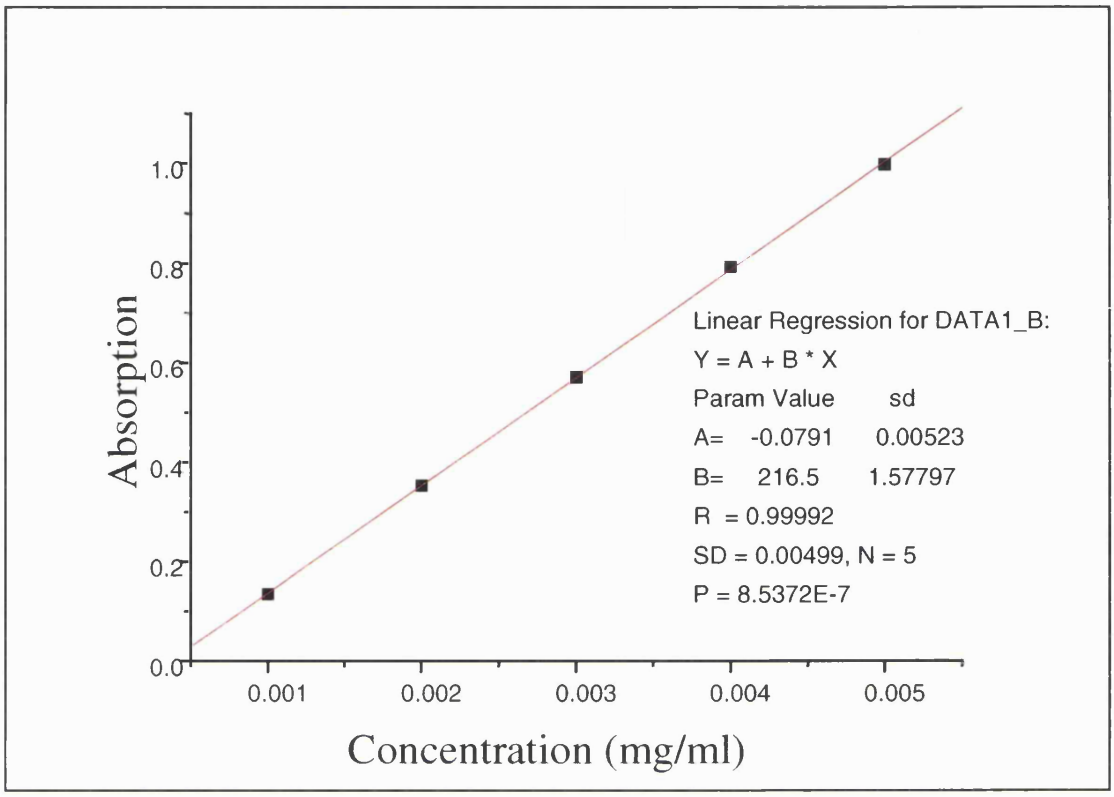



**Figure 5.1**. Calibration curve for chlorpheniramine maleate.

## *5.3. Results*

### 5.3.1. Effect of mixing time on drug homogeneity of binary and ternary powder mixes containing Emcocel 50M

Chlorpheniramine maleate (CM) was used as a model drug at 1% concentration and mixed separately with Emcocel 50M (EM50M), Prosolv50M (P50M) to form binary mixes. Binary mixes of EM50M were followed by addition of 2% colloidal silica (CS) to form ternary mixes (lab mix 50M). Figure 5.2 shows the relationship between mixing time and coefficient of variation (CV) for different powder mixes investigated. The mean particle size ($d50^{th}$) of Emcocel 50M is 65 μm. The figure clearly illustrates, for the three powder mixes investigated, that as the mixing time increases CV decreases to a critical point beyond which, longer mixing results in de-mixing (increase in CV). This is more evident in the case of the lab mix 50M, although a low CV (approximately 4%) was reached after only 5 minutes. Interestingly, an optimal drug homogeneity (approximately 4%) was obtained in 15 minutes compared 30 minutes following the use of Prosolv50M and Emcocel 50M, respectively. Therefore, for a particular powder system, it is critical to optimise mixing time to ensure maximum drug homogeneity and uniformity.

A satisfactory degree of mixing occurred within different times of mixing for different powder mixes investigated. For EM50M binary mixes time of mixing required to achieve minimum CV (3.43%) was 30 minutes. For P50M and L50M it was equal to 15 minutes (CV = 4.23%) and 5 minutes (CV = 3.98%), respectively. It is expected that, at mixing times which correspond to minimal CV, equilibrium exists between mixing and segregation (de-mixing) which led to such high degree of mixing.

| Name of sample | Time Mix (min) | %C.V |
|---|---|---|
| Emcocel 50M | 1 | 15.45 |
| | 5 | 8.37 |
| | 15 | 4.87 |
| | 30 | 3.43 |
| | 60 | 7.17 |
| | | |
| Prosolv50M | 1 | 22.04 |
| | 5 | 8.78 |
| | 15 | 4.23 |
| | 30 | 4.99 |
| | 60 | 8.12 |
| | | |
| Lab mix50M | 1 | 7.78 |
| | 5 | 3.98 |
| | 15 | 5.63 |
| | 30 | 8.58 |
| | 60 | 4.76 |

**Table 5.1.** Effect of mixing time on drug homogeneity of binary and ternary powder mixes containing Emcocel 50M series.

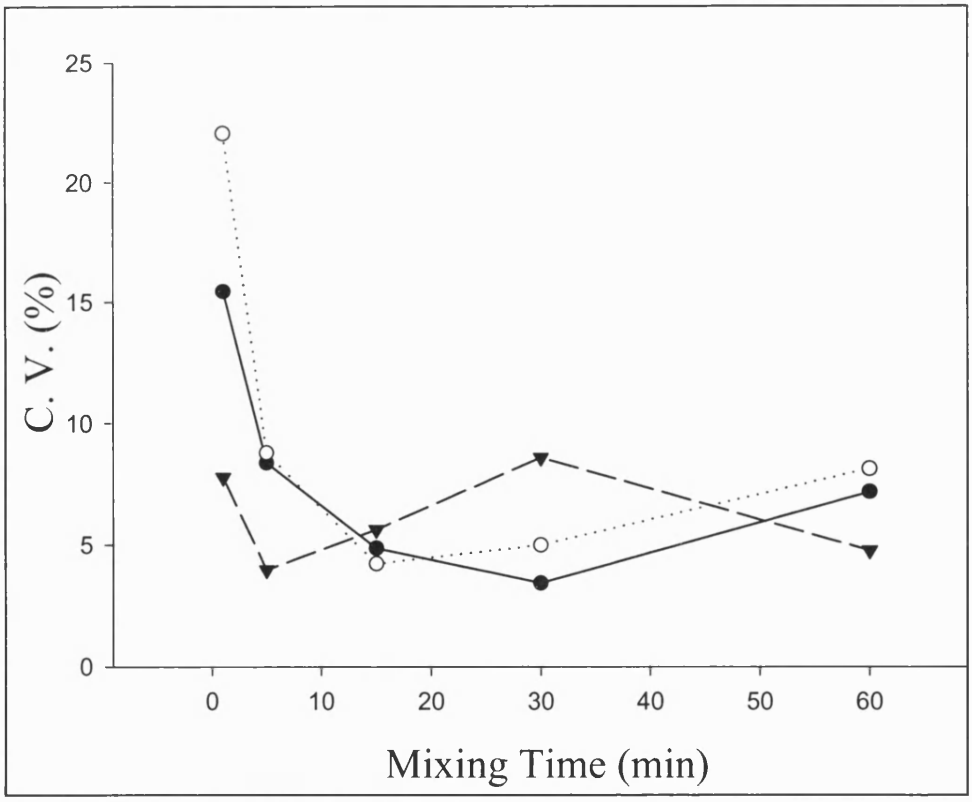



**Figure 5.2.** Effect of mixing time on drug homogeneity for binary and ternary powder mixes containing Emcocel 50M (●), Prosolv50M (○) and lab mix 50M (▼).

### 5.3.2 Effect of mixing time on drug homogeneity of binary and ternary powder mixes containing Emcocel 90M

Figure 5.3. shows the effect of mixing time on drug homogeneity of powder mixes containing Emcocel 90M (Emcocel 90M, Prosolv90M and lab mix 90M). The particle size of Emcocel 90M is 90-100 μm as shown in chapter 2. A similar mixing trend to that recorded for the powder mixes containing Emcocel 50M was observed. An acceptable degree of mixing has occurred at different times of mixing for different powder mixes investigated. For Emcocel 90M binary mixes, time of mixing required to achieve minimum CV (3.72%) was 30 minutes. For Prosolv90M and lab mix 90M it was equal to 15 minutes (CV = 4.34%) and 5 minutes (CV = 4.78), respectively. As data show, times to achieve satisfactory degrees on mixing (minimum CV) were comparable for powder mixes containing Emcocel 50M or Emcocel 90M. There is, once again, a direct correlation between the improved flowability of modified grades of MCC and the initial results.

| Name of sample | Time Mix (min) | %C.V |
|---|---|---|
| Emcocel90M | 1 | 7.20 |
| | 5 | 4.42 |
| | 15 | 4.35 |
| | 30 | 3.72 |
| | 60 | 5.61 |
| | | |
| Prosolv90M | 1 | 7.04 |
| | 5 | 4.84 |
| | 15 | 4.34 |
| | 30 | 7.62 |
| | 60 | 9.30 |
| | | |
| Lab mix 90M | 1 | 7.72 |
| | 5 | 4.78 |
| | 15 | 4.95 |
| | 30 | 7.95 |
| | 60 | 5.14 |

**Table 5.2.** Effect of mixing time on drug homogeneity of binary and ternary powder mixes containing Emcocel 90M series.

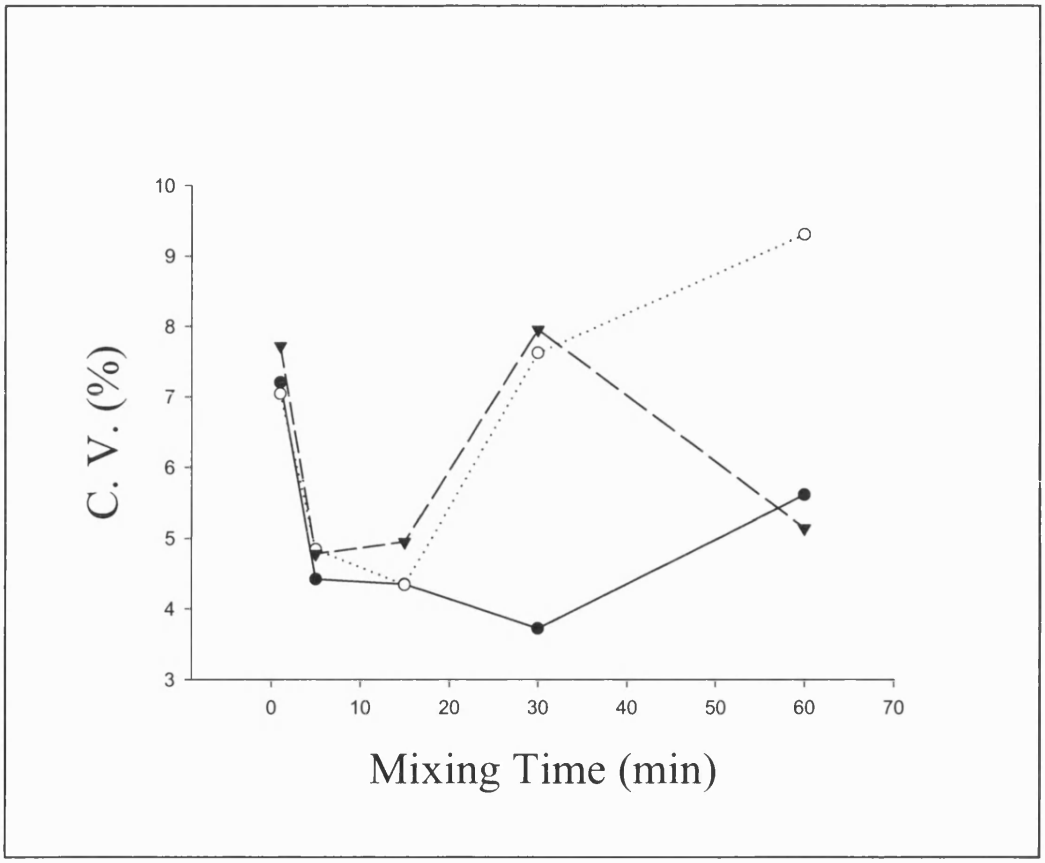



**Figure 5.3.** Effect of mixing time on drug homogeneity for binary and ternary powder mixes containing Emcocel 90M (●), Prosolv90M (○) and lab mix 90M (▼).

### 5.3.3. Effect of mixing time on drug homogeneity of binary powder mixes containing Emcompress 200 and Lactose D30

Chlorpheniramine maleate (CM) was used as a model drug at 1% concentration and mixed with Emcompress200 (EM) and Lactose L30D (L30D) to form binary mixes. Figure 5.4. shows the effect of mixing time on drug homogeneity of powder mixes containing Emcompress (EMC) and Lactose 30D (L30D). As for other powder mixes investigated, an increase in mixing time has resulted in a decrease in CV and improvement in content uniformity. However, the satisfactory degree of mixing was not achieved for both excipients. Mixing times required to achieve minimum CV for powder mixes containing EMC and L30D were 60 minutes with CV of 8.39% and 8.03%, respectively. These results indicate that, relatively, microcrystalline cellulose forms ordered blends more quickly than EMC and L30D. This is a beneficial feature for these excipients. The reasons for this benefit are unclear. The higher bulk density of both EMC and L30D might be expected to helpful in forming ordered mixes, as increased density may break up agglomerates of drug material. However, for larger particle size material such as chlorpheniramine maleate (65μm), this benefit may be less important. Under these conditions the improved flow of these materials may be important, however the triboelectric series data may be helpful in explaining the results.

| Name of sample | Time Mix (min) | %C.V |
|---|---|---|
| Emcompress 200 | 1 | 20.59 |
| | 5 | 32.35 |
| | 15 | 9.32 |
| | 30 | 12.43 |
| | 60 | 8.39 |
| | | |
| Lactose D30 | 1 | 22.99 |
| | 5 | 9.21 |
| | 15 | 9.74 |
| | 30 | 12.54 |
| | 60 | 8.03 |

**Table 5.3.** Effect of mixing time on drug homogeneity of binary and ternary powder mixes containing Emcompress200 and LactoseD30

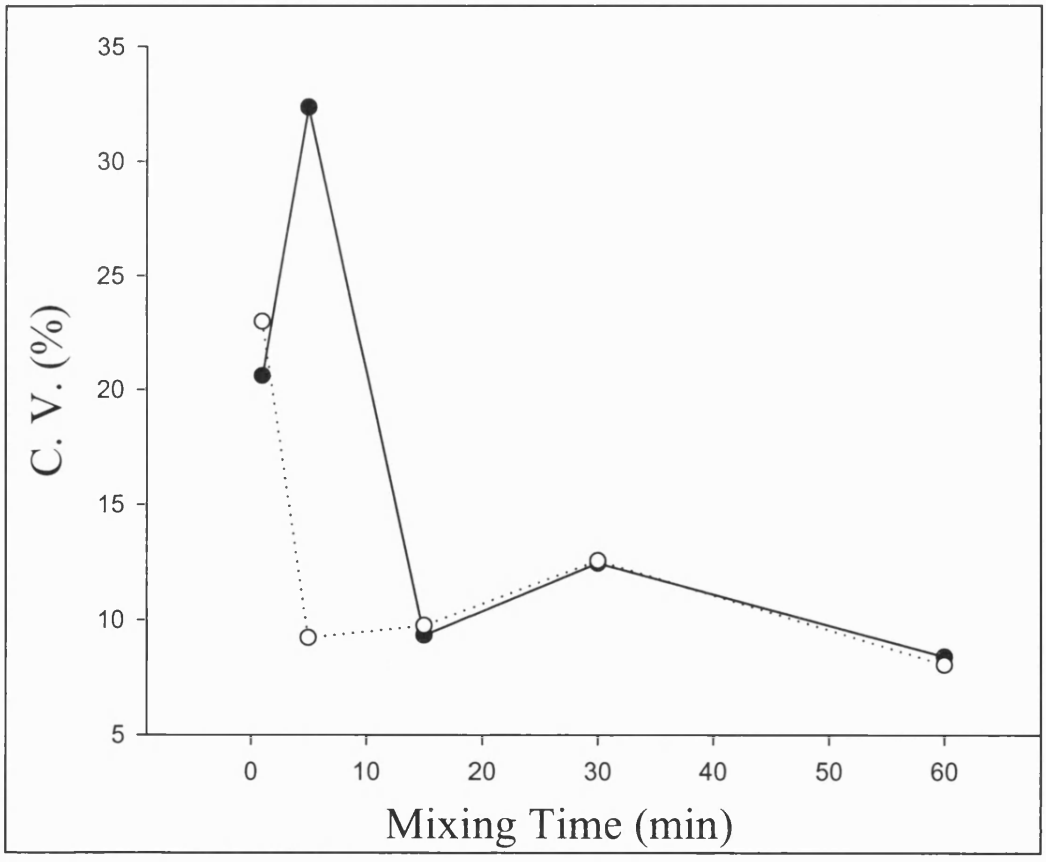



**Figure 5.4.** Effect of mixing time on Drug homogeneity for binary powder mixes containing Emcompress 200 (●) and Lactose D30 (○).

### 5.3.4. Effect of mixing time on electrostatic charge properties of binary and ternary

The homogeneity and physical stability of ordered mixes were found to be dependent upon the electrostatic charges developed on component materials during mixing (Staniforth and Rees, 1982). Therefore, it was thought that it would be rational to investigate the effect of mixing on electrostatic charge properties of powder mixes. The effect of mixing time on the mean specific charge of the same powder mixes was investigated following flow on different chutes (i.e. metal, plastic and treated plastic), data are summarized in Tables 5.4, 5.5 and 5.6 respectively.

**Table 5.4.** Effect of mixing time (min) on the mean specific charges ($C.g^{-1}X10^{-9}$) CV% of different powder mixes investigated following flow on a metal chute:

| Mixing time / Sample | 1 | | 5 | | 15 | | 30 | | 60 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Emcocel50M | 1.51 | 34.37 | 2.37 | 9.44 | 2.13 | 17.68 | 2.99 | 4.68 | 2.93 | 5.81 |
| Emcocel90M | 2.90 | 36.99 | 2.98 | 6.82 | 3.54 | 7.06 | 3.81 | 5.22 | 3.63 | 3.84 |
| Prosolv 50M | 2.58 | 27.14 | 2.24 | 20.16 | 3.50 | 3.87 | 5.46 | 7.85 | 3.50 | 2.05 |
| Prosolv 90M | 3.57 | 9.83 | 3.58 | 5.17 | 4.84 | 4.19 | 5.93 | 4.62 | 6.33 | 7.78 |
| Lab mix50M | 2.55 | 43.10 | 2.32 | 33.65 | 2.24 | 39.49 | 2.97 | 34.97 | 3.63 | 19.05 |
| Lab mix90M | 0.56 | 50.57 | 1.46 | 33.34 | 2.18 | 36.00 | 3.61 | 35.12 | 4.33 | 18.57 |
| Emcompress | 0.36 | 46.57 | 0.45 | 30.88 | 0.50 | 33.19 | 0.33 | 31.75 | 0.41 | 41.74 |
| Lactose D30 | 0.98 | 25.64 | 0.99 | 13.28 | 1.04 | 17.28 | 1.17 | 12.14 | 1.10 | 24.74 |

**Table 5.5**. Effect of mixing time (min) on the mean specific charges ($C.g^{-1}X10^{-9}$) CV% of different powder mixes investigated following flow on a plastic chute:

| Mixing time (minutes) | 1 | | 5 | | 15 | | 30 | | 60 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sample | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Emcocel50M | 8.59 | 29.43 | 5.51 | 30.02 | 3.77 | 26.76 | 6.12 | 12.46 | 3.45 | 25.82 |
| Emcocel90M | 5.77 | 40.01 | 7.08 | 35.98 | 4.11 | 35.29 | 3.07 | 29.94 | 2.60 | 28.37 |
| Prosolv50M | 2.68 | 38.97 | 3.86 | 45.62 | 1.93 | 33.60 | 2.06 | 30.00 | 4.15 | 12.66 |
| Prosolv90M | 4.84 | 32.21 | 2.93 | 34.79 | 2.33 | 37.66 | 2.67 | 22.18 | 3.76 | 28.76 |
| Lab mix 50M | 0.77 | 37.77 | 2.39 | 39.42 | 2.27 | 39.22 | 1.38 | 31.04 | 1.29 | 34.57 |
| Lab mix 90M | 3.05 | 32.35 | 3.09 | 37.56 | 2.17 | 34.36 | 2.29 | 30.57 | 3.08 | 31.34 |
| Emcompress | 2.00 | 39.11 | 2.02 | 21.36 | 2.41 | 17.73 | 2.30 | 20.71 | 3.17 | 34.24 |
| LactoseD30 | 3.73 | 39.00 | 3.07 | 17.59 | 5.00 | 22.27 | 4.22 | 17.51 | 3.50 | 12.42 |

**Table 5.6**. Effect of mixing time (min) on the mean specific charges ($C.g^{-1}X10^{-9}$) CV% of different powder mixes investigated following flow on a treated plastic chute

| Mixing time (minutes) | 1 | | 5 | | 15 | | 30 | | 60 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sample | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Emcocel50M | 0.71 | 33.83 | 2.02 | 33.12 | 1.50 | 32.34 | 1.52 | 28.18 | 1.49 | 24.76 |
| Emcocel90M | 1.55 | 38.09 | 1.54 | 38.74 | 1.61 | 32.80 | 1.92 | 28.12 | 1.87 | 38.10 |
| Prosolv50M | 3.41 | 33.69 | 2.70 | 32.37 | 2.49 | 18.54 | 2.36 | 15.37 | 4.19 | 12.45 |
| Prosolv90M | 5.68 | 38.37 | 4.76 | 15.08 | 6.25 | 20.20 | 6.05 | 17.56 | 5.42 | 18.24 |
| Lab mix 50M | 0.51 | 41.88 | 0.23 | 37.42 | 0.28 | 25.26 | 0.43 | 27.00 | 0.41 | 25.57 |
| Lab mix 90M | 1.36 | 37.68 | 1.35 | 23.52 | 0.60 | 25.14 | 0.70 | 24.29 | 0.59 | 30.71 |
| Emcompress. | 0.69 | 35.27 | 0.93 | 21.03 | 0.78 | 20.15 | 0.56 | 17.75 | 0.96 | 26.88 |
| LactoseD30 | 1.63 | 38.08 | 1.03 | 30.47 | 2.01 | 27.97 | 1.25 | 27.06 | 1.90 | 28.74 |

Following flow on a metal chute all powder mixes investigated (Emcocel 50M, lab mix 50M and Prosolv50M) acquired electronegative charges. Following flow on a plastic chute such powder mixes acquired electropositive charges. However, the same powder mixes acquired electronegative charges following flow on a treated plastic chute. Staniforth and Rees, (1982c) reported that excipient powders generally charged electronegatively when contacted with metal or glass surfaces whereas they charged electropositively when contacted with plastic surfaces. In addition, triboelectrically charged powders were found to acquire a positive or negative charge according to work function of the powder molecules in relation to that of a cyclone wall (Staniforth and Rees, 1981, 1982b). A general observation, which can be made, is related to the reproducibility achieved. For the majority of powders tested, the calculated %CV values obtained from the metal chute determinations (<20%) were smaller than those obtained with the plastic chute (10-45%). Electrostatic charges arise as the separation of positive and negative charges at the interface between two dissimilar surfaces. When powder particles move along the vibrating chute, an equal and opposite charge is left on the chute. The metal chute is a conductor; therefore, the developed charge will be consistently redistributed to earth. The plastic chute, however, is an insulator and the developed charge will remain on the surface due to difficulty of free electron movement. Consequently, the charge retained on the plastic chute will influence the subsequent determinations. In general, the effect of mixing time on the mean specific charges was not significant. However the effect of mixing time on the reproducibility between different determinations (CV) was marked after flow on a metal chute. Such an effect was a function of the powder mix together with the type of Emcocel used (Emcocel 50M or Emcocel 90M). For the binary mix of Emcocel 50M, mixing between 1 to 60 minutes resulted in a decrease in CV from 34% to 6%, respectively. For the Emcocel 90M powder mix and for the same time period the CV

decreased from 36% to 4%, respectively. A similar trend was observed for the powder mixes of Prosolv50M and Prosolv90M. For Prosolv50M, following mixing between 1 to 60 minutes, CV decreased from 27% to 2%, respectively table 5.4. Compared to the Emcocel 50M, Emcocel 90M and Prosolv50M, the Prosolv90M powder mixes exhibited higher reproducibility (lower CV) between different determinations at most of different mixing times. For example, after 1 minute mixing of Prosolv90M, CV between different determinations was only 10% compared to 34%, 36% and 27% for Emcocel 50M, Emcocel 90M and Prosolv50M, respectively. Both Prosolv50M and Prosolv90M are based on silicified microcrystalline cellulose (SMCC). However, Prosolv90M consist of Emcocel 90M, which has a mean particle size of 90-100m compared to 65 μm for Prosolv50M. Such larger particles ensure a better flow, which gives reason for good reproducibility of charge determinations. For lab mix 50M and lab mix 90M powder mixes the reproducibility between different determinations improved following longer mixing time, however, such reproducibility was far less compared to the other powder mixes investigated. As mentioned above in 5.2.3.3 lab mix 50M and lab mix 90M were prepared by physical mixing of Emcocel 50M and chlorpheniramine maleate and colloidal silica. The distribution of colloidal silica was not uniform as shown by SEM as mentioned earlier in chapter two. Colloidal silica exists as agglomerates at the surface of microcrystalline cellulose (Emcocel). Longer mixing results in shearing and thereby, de-agglomeration of colloidal silica, which may have improved uniformity and distribution of the glidant. This may explain the improvement in reproducibility between determinations after longer mixing times. In the cases of Prosolv50M and Prosolv90M colloidal silica was co-processed with MCC (silicified MCC). This results in intimate association of colloidal silica and MCC, and consequently, these mixes showed superior physical characteristics (e.g. flow). This explains the good reproducibility between different determinations for

powder mixes of Prosolv50M and Prosolv90M compared to other powder mixes investigated.

### 5.3.5. Effect of mixing time on drug homogeneity (CV) of binary mixes containing Emcocel 50M/CM and Emcocel 90M/CM following addition of magnesium stearate

| Name of sample | Time Mix (min) | C.V |
|---|---|---|
| Emcocel 50M | 1 | 24.87 |
| | 5 | 19.78 |
| | 15 | 15.08 |
| | 30 | 5.13 |
| | 60 | 6.07 |
| | | |
| Emcocel 90M | 1 | 28.72 |
| | 5 | 15.67 |
| | 15 | 4.07 |
| | 30 | 2.48 |
| | 60 | 12.04 |

**Table 5.7.** Effect of mixing time on drug homogeneity of ternary powder mixes containing Emcocel 50M and Emcocel 90M.

Figure 5.5 illustrates the effect of mixing time on drug homogeneity (CV) for binary mixes containing Emcocel 50M or Emcocel 90M,with chlorpheniramine maleate before and after addition of magnesium stearate. The results show a dramatic de-stabilizing effect of magnesium stearate on drug homogeneity (CV) of the powder mixes investigated. For Emcocel 50M binary system addition of magnesium stearate results in an increase of CV from 16% to 24% after mixing for 1 minute. Longer mixing with magnesium stearate caused further de-stabilization of the binary mixes. After mixing for 5 minutes, CV for Emcocel 50M powder mixes increased from 8% before addition of magnesium stearate to 19% after addition of the lubricant and mixing for 5 minutes. Addition of magnesium

stearate also results in de-stabilization of binary system of Emcocel 90M as illustrated in figure 5.5. The observed behaviour and the layer structure of the magnesium stearate crystal suggest that the lubricant shears off during mixing and is probably adsorbed at the surfaced of the carrier particles. This phenomenon of film formation by magnesium stearate during mixing is consistent with the observation of (Bolhuis et al., 1975). Magnesium stearate was shown by Staniforth and Ahmed (1986,1987); and Ahmed, (1989), to interfere with the binary mixes of KCl and sucrose-based excipients which resulted in de-stabilization of such systems. In the present study a similar drug stripping mechanism may explain the de-stabilizing action found with magnesium stearate. The stripping effect of magnesium stearate is shown schematically in figure 5.24. During mixing, de-agglomeration of magnesium stearate takes place, followed by the formation of a near-continuous monoparticulate hydrophobic film around Emcocel and chlorpheniramine maleate adhesive (ordered) units and leading to displacement of CM particles from their binding sites on the carrier particles, perhaps as a result of surface charge interactions. Magnesium stearate was found to acquire an electropositive charge following flow on a metal and electronegative on plastic chutes as mentioned earlier in chapter two. For this reason, there should be a greater affinity between magnesium stearate and the carrier surfaces with consequent displacement of previously adhering drug particles. It is known that the cohesive forces within magnesium stearate are less than its adhesive properties to a wide range of materials, leading to highly efficient spreading of the stearate on most pharmaceutical materials and surfaces. For this reason any displaced drug particles would be attracted to free particles of the lubricant (figure 5.24) causing a further disrupting effect on homogeneous drug disposition in the blend.

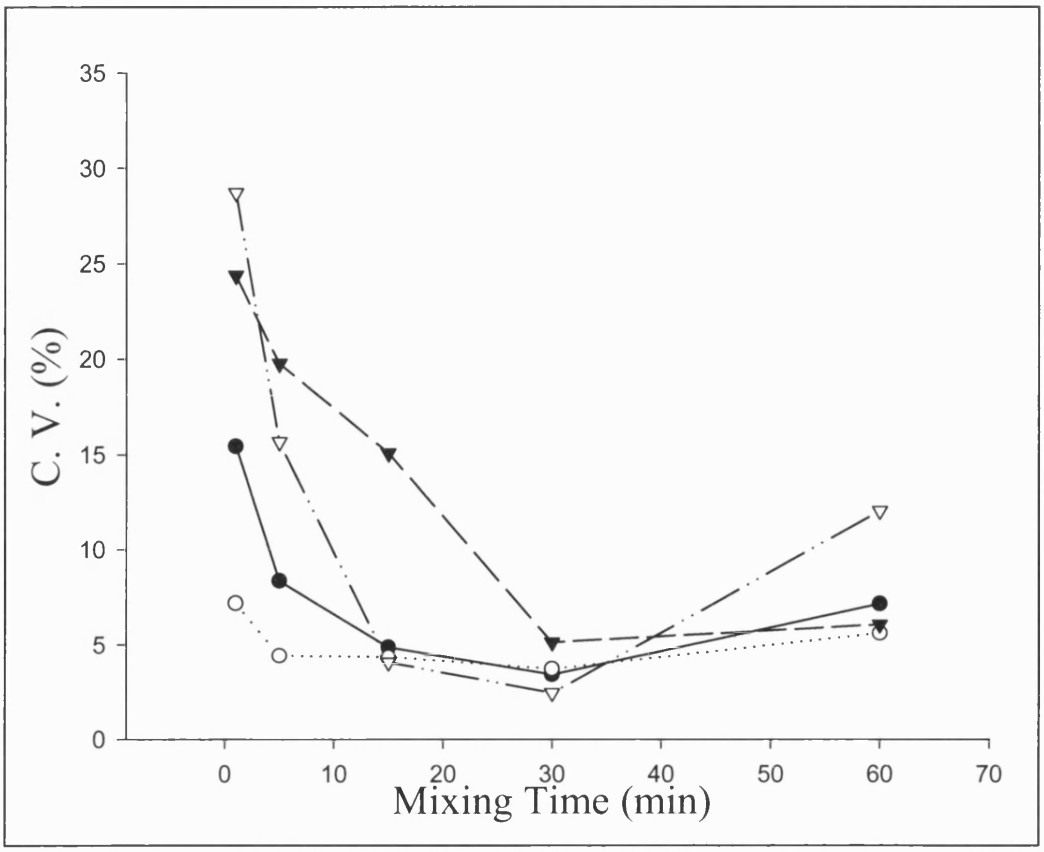



**Fig 5.5** Effect of mixing time on drug homogeneity (CV) for binary mixes containing E50M/CM and E90M/CM before and after addition of magnesium stearate. Emcocel 50M (●), Emcocel 90M (○), Emcocel 50M/ magnesium stearate (▼) and Emcocel 90M/ magnesium stearate (▽).

### 5.3.6. Effect of mixing time on drug homogeneity (CV) for ternary mixes containing lab mix 50M /CM/CS, Prosolv50M /CM, Prosolv90M /CM and lab mix 90M /CS/CM following addition of magnesium stearate.

| Name of sample | Time Mix (min) | %C.V |
|---|---|---|
| Lab mix 50M | 1 | 8.58 |
| | 5 | 8.51 |
| | 15 | 6.35 |
| | 30 | 14.11 |
| | 60 | 31.76 |
| | | |
| Lab mix 90M | 1 | 7.74 |
| | 5 | 2.43 |
| | 15 | 7.38 |
| | 30 | 3.78 |
| | 60 | 6.04 |

**Table 5.8.** Effect of mixing time on drug homogeneity of ternary powder mixes containing lab mix Emcocel 50M and lab mix Emcocel 90M.

| Name of sample | Time Mix (min) | %C.V |
|---|---|---|
| Prosolv50M | 1 | 21.08 |
| | 5 | 5.34 |
| | 15 | 6.35 |
| | 30 | 3.89 |
| | 60 | 4.20 |
| | | |
| Prosolv90M | 1 | 9.92 |
| | 5 | 3.65 |
| | 15 | 3.34 |
| | 30 | 8.01 |
| | 60 | 7.88 |

**Table 5.9.** Effect of mixing time on drug homogeneity of ternary powder mixes containing Prosolv50M and Prosolv90M.

Figure 5.6 illustrates the effect of mixing time on drug homogeneity (CV) for ternary mixes containing Emcocel 50M, or Emcocel 90M with chlorpheniramine maleate and colloidal silica (CS) (lab mix 50M) or (lab mix 90M) before and after addition of magnesium stearate. Ahmed and Staniforth, (1987), found that colloidal silica re-stabilizes ternary systems containing a sucrose-based excipient/KCl and magnesium stearate. Colloidal silica exerts its re-stabilizing effect by an "enrobement" mechanism as shown in figure 5.23 Ahmed, (1987) where colloidal silica due to the extensive difference in surface also compared to magnesium stearate (187 $m^2/g$ to 12 $m^2/g$) encircles the magnesium stearate particles preventing them from stripping the drug particles. In the present example, however, magnesium stearate caused de-stabilization of the lab mix despite the presence of colloidal silica. The explanation of this seemingly anomalous result is based on the order of addition of these components. In the present study magnesium stearate was added following addition of the CS. This resulted in de-stabilization of the powder mix. However, addition of colloidal silica to a de-stabilized system containing magnesium stearate resulted in re-stabilization of the system (Ahmed, 1987). As discussed above the re-stabilizing effect of colloidal silica is based on an enrobement mechanism, which in turns is based on the formation of a glidant film around the lubricant particles. Therefore, the formation of such film is basically essential for the re-stabilizing effect to take place. This may be evident in the case of the Prosolv50M (figure 5.7). In this case the addition of MS to the powder mix containing Prosolv50M and chlorpheniramine maleate does not result in de-stabilization of such a powder system. This may be due to the fact that Prosolv50M is manufactured by spray drying of Emcocel and colloidal silica, therefore colloidal silica exists as non-continuous layer of individual particles around the carrier system. The presence of such particles prevents magnesium stearate from de-stabilizing this system.

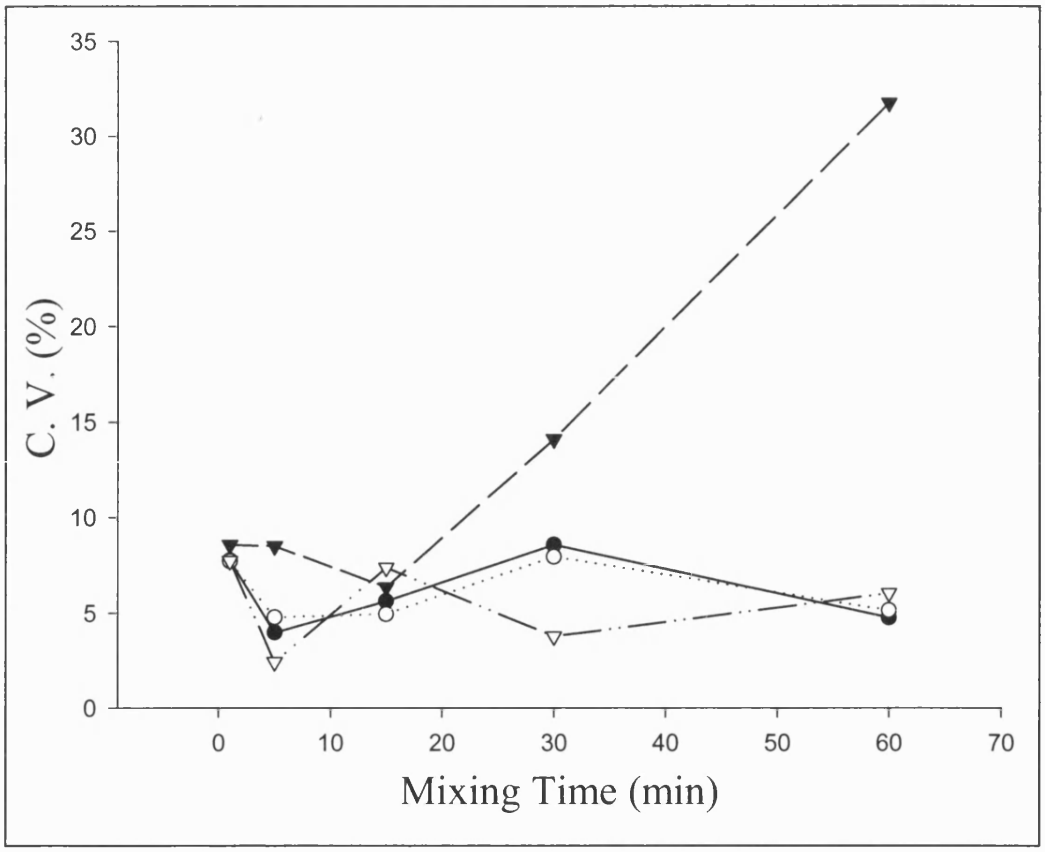



**Fig 5.6:** Effect of mixing time on drug homogeneity (CV) for ternary mixes containing E50M/CS/CM (L50M) and E90M/CS/CM (L90M) before and after addition of magnesium stearate. lab mix Emcocel 50M (●), lab mix Emcocel 90M (○), lab mix Emcocel50M/ magnesium stearate (▼)and lab mix Emcocel 90M/ magnesium stearate (▽).

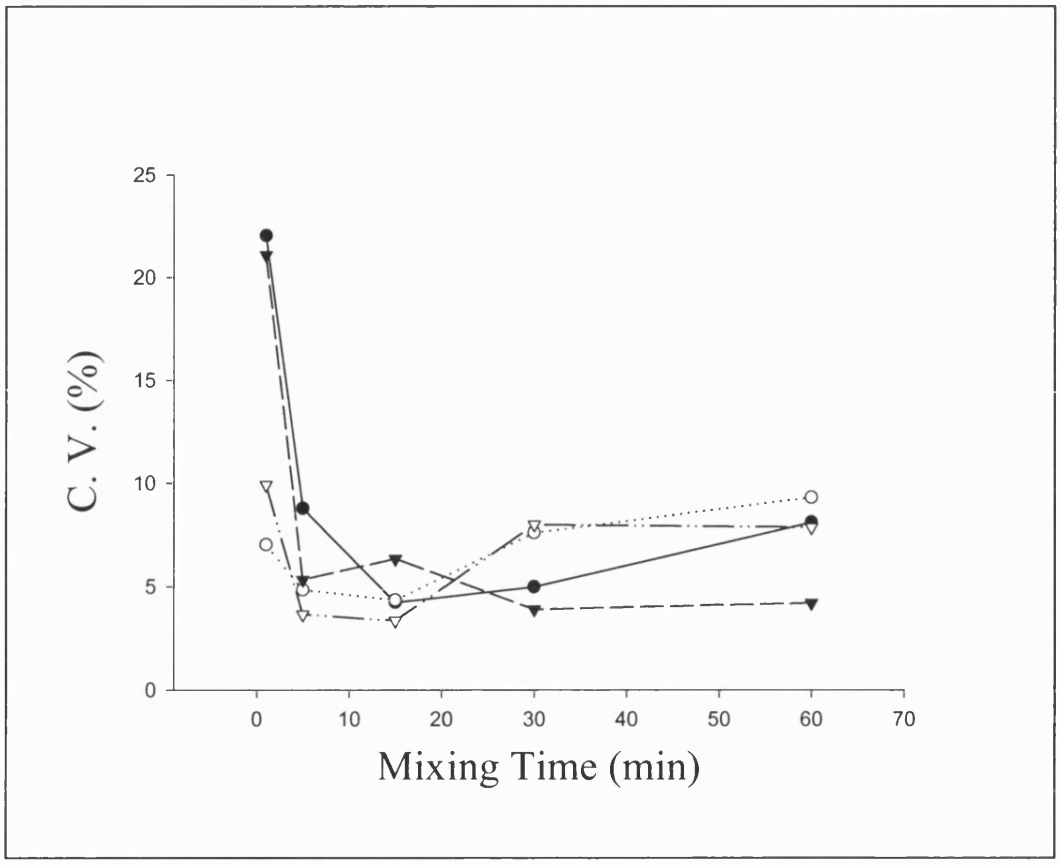



**Fig 5.7.** Effect of mixing time on drug homogeneity (CV) for binary mixes containing Prosolv50M/Chlorpheniramine and Prosolv90M/Chlorpheniramine maleate before and after addition of magnesium stearate. Prosolv50M (●), Prosolv90M (○), Prosolv50M/ magnesium stearate (▼)and Prosolv90M/ magnesium stearate (▽).

### 5.3.7. Effect of mixing time on drug homogeneity (CV%) for binary mixes for Emcompress200 /CM and Lactose D30 /CM following addition magnesium stearate

Table 5.10 with figures 5.8 and 5.9 show the effect of mixing time on drug homogeneity of powder mixes containing Emcompress200 and Lactose D30 following addition of magnesium stearate.

Figure 5.8, illustrates the effect of mixing time on drug homogeneity (CV%) for binary mixes containing Emcompress200 with Chlorpheniramine maleate before and after addition of magnesium stearate. The results show a dramatic de-stabilizing effect of magnesium stearate on drug homogeneity (CV) of the powder mixes investigated. Emcompress200 binary system addition of magnesium stearate results in an increase of CV from (20.59%) to (29.69%) after mixing for 1 minute. While from 5 to 30 minute there is stabilizing effect of magnesium stearate. Longer mixing with magnesium stearate caused further de-stabilization of the binary system.

Figure 5.9, illustrates the effect of mixing time on drug homogeneity (CV%) for binary mixes containing LactoseD30 with Chlorpheniramine maleate before and after addition of magnesium stearate. The results show a dramatic de-stabilizing effect of magnesium stearate on drug homogeneity (CV) of the powder mixes investigated. LactoseD30 binary system addition of magnesium stearate results in an increase of CV from (22.99%) to (36.81%) after mixing for 1 minute and from (9.21%) to (15.73%) after 5minute. Longer mixing with magnesium stearate caused further de-stabilization of the binary system. The de-stabilization effect of magnesium stearate on Lactose D30 may attributed to the relatively small particle size compared to Emcompress200. For both Emcompress200 and

LactoseD30 the minimum CV% occurred after 60 minute of mixing time (7.78% and 12.77%).

| Name of sample | Time Mix (min) | C.V |
|---|---|---|
| Emcompress 200 | 1 | 29.69 |
| | 5 | 27.14 |
| | 15 | 10.58 |
| | 30 | 17.59 |
| | 60 | 7.78 |
| | | |
| Lactose D30 | 1 | 36.81 |
| | 5 | 15.73 |
| | 15 | 31.40 |
| | 30 | 18.03 |
| | 60 | 12.77 |

**Table 5.10.** Effect of mixing time on drug homogeneity of ternary powder mixes containing Emcompress 200 or Lactose D30.

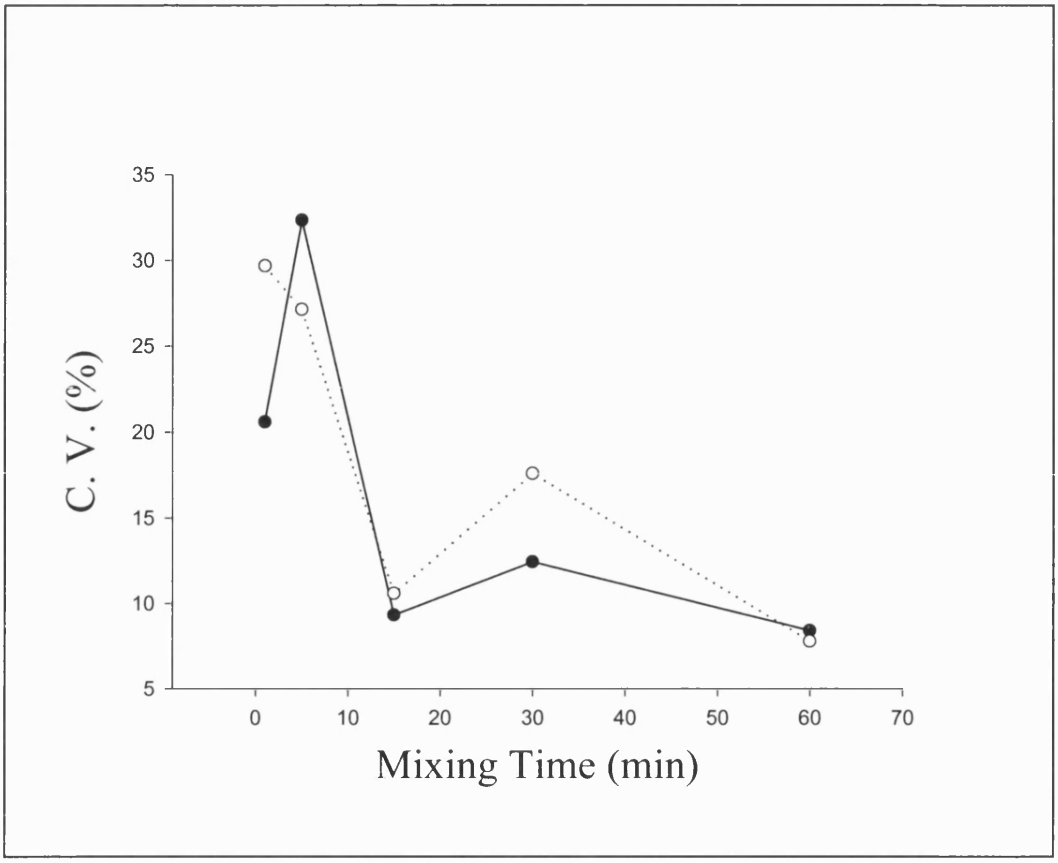



**Fig 5.8.** Effect of mixing time on drug homogeneity (CV) for binary mixes containing Emcompress200/Chlorpheniramine maleate before and after addition of magnesium stearate. Emcompress 200 (●) and Emcompress200/ magnesium stearate (○).

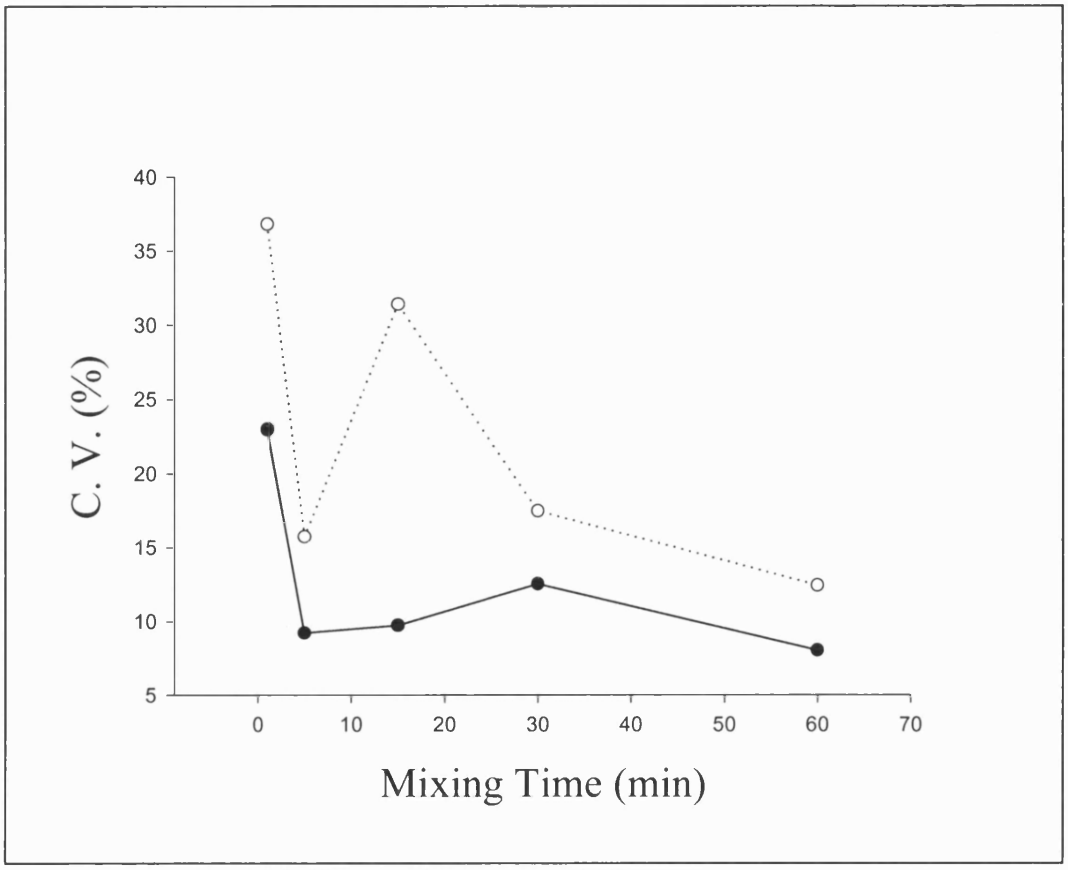



**Fig 5.9.** Effect of mixing time on drug homogeneity (CV) for binary mixes containing Lactose D30/Chlorpheniramine maleate before and after addition of magnesium stearate. Lactose D30 (●) and Lactose D30/ magnesium stearate (○).

### 5.3.8. Effect of mixing time on the electrostatic charge

*5.3.8.1. Effect of mixing time on coefficient of variation (CV) and electrostatic charges properties of pharmaceutical powder mixes*

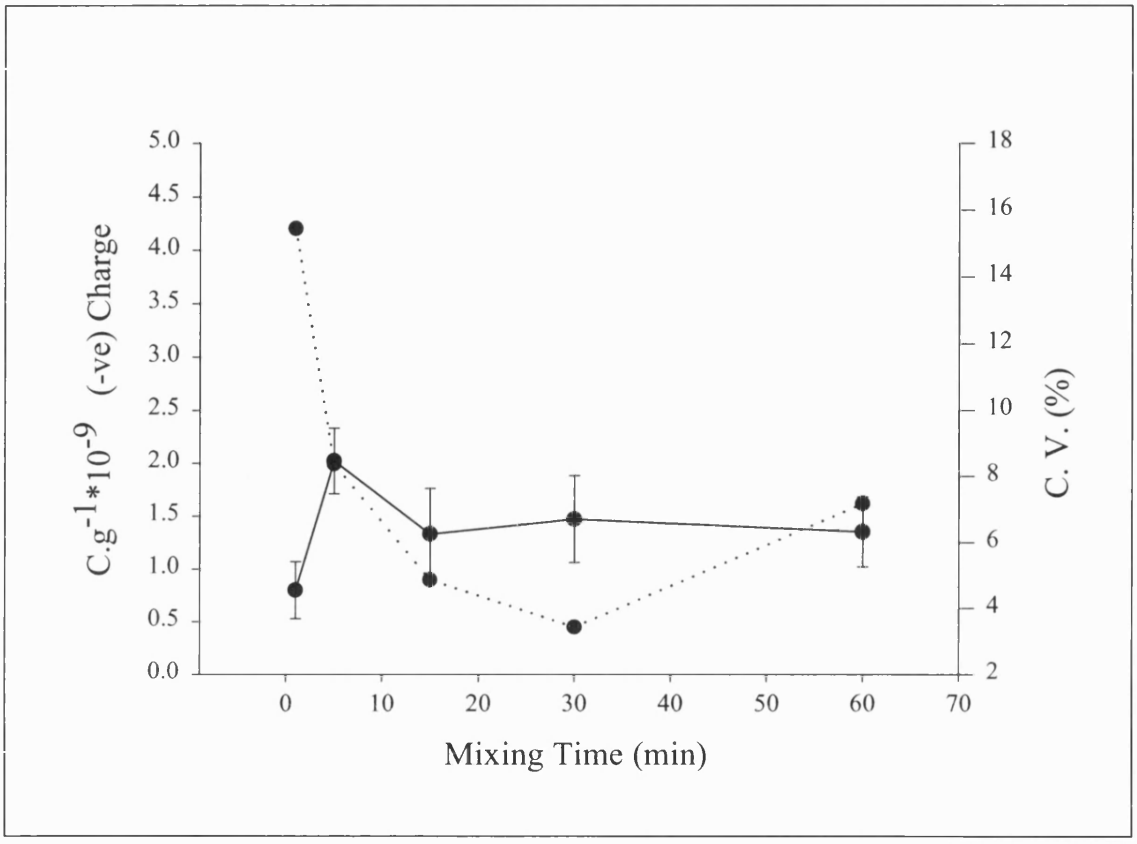



**Fig. 5.10.** Correlation between mixing time and CV and mean specific charge for Emcocel 50M following flow of the powder mix on a treated plastic chute.

(_____) charge and (.....) C.V.

Figure 5.10. shows the relationship between mixing time, CV and mean specific charge for Emcocel 50M following flow of the powder mix on a treated plastic chute. The figure clearly illustrates that as the mixing time increases CV decreases to a critical point beyond which, longer mixing results in de-mixing (increase in CV). This is not unexpected, since mixing and segregation (de-mixing) exist in a dynamic equilibrium. The figure also shows the effect of mixing time on the mean specific charge of the same excipient. As mentioned above the electrostatic charges were measured using a Faraday well after allowing the powder to flow over treated plastic surface. Following mixing for different times (between 1 to 60 minutes) the powder mix acquired electronegative charges, which significantly increased, in magnitude, at the beginning (1 to 5 minutes). Longer mixing, however, did not result in any further increase in the magnitude of the acquired charges. At the beginning of mixing using the Turbula mixer the excipient (Emcocel) de-agglomerates which may have resulted in increase in surface area available and therefore, greater opportunity for charging. However, no further de-agglomeration takes place with no significant change in the electrostatic charge properties of the powder.

Figures from 5.11.-5.15. show the relationship between mixing time, CV and the mean specific charge for the lab. mix 50M (Emcocel 50M + chlorpheniramine maleate + Aerosil 200), Prosoolv50M + CM, Emcocel 90M + CM, lab mix 90M + CM and Prosolv90M + CM following flow of the powder mix on a treated plastic chute.

The figure 5.11. (lab mix Emcocel 50M + CM) clearly shows that with time the CV decreases to a critical point (5 minutes) beyond which, longer mixing results in de-mixing. During the same time interval there was a significant decrease in the magnitude of the mean specific charge. Longer mixing results in no improvement in drug homogeneity and content uniformity with no significant change in the electrostatic charge. A possible explanation for this phenomenon is that the agglomerates of the Emcocel were encircled with fine particles of Aerosil 200, due to the large difference in surface area (183 $m^2/g$ to 1.5 $m^2/g$).

Figure 5.12. (Prosolv50M + Chlorpheniramine Maleate) shows that with time the CV decreases to a critical point (15 minutes) beyond which, longer mixing results in de-mixing. The figure also shows the effect of mixing time on the mean specific charge. Unlike the previous example of lab mix50M (figure 5.11), during the period of mixing between 5 min to 30 min there was no significant change in the electrostatic charge of the powder mix. Prosolv is a co-processed microcrystalline cellulose and colloidal silica. A spray drying procedure was used to prepare such product. Therefore, there is an intimate mix between MCC and CS. Thus, longer mixing did not result in a significant decrease in electrostatic charges, only after 30 minutes. In contrast, the lab mix 50M and due to the presence of CS on the surface of the MCC, longer mixing will result in shearing of the CS agglomerates and the formation of a continuous film as described in the previous examples.

In figure 5.13 (Emcocel 90M + CM), as explained earlier, as mixing proceeds CV decreases until a dynamic equilibrium is achieved (30 minutes) after which de-mixing occurs. As for Emcocel 50M following mixing for different times (between 1 to 60 minutes) the powder mix acquired electronegative charges. Unlike Emcocel 50M, an increase in mixing did not result in any significant increase in the magnitude of the acquired charges. The mean particle size of Emcocel 90M is about 90-100 μm and at this range of particle size the excipient exists as a free flowing powder with no agglomerated particles. Particle interactions are mainly driven by gravitational forces and less by electrical forces. In contrast, particle interactions in Emcocel 50M are less affected by gravitational forces but more by electrical forces, which causes agglomeration of the powder.

In figure 5.14. lab mix 90M (Emcocel 90M + Chlorpheniramine Maleate + Aerosil 200), following 5 minutes mixing there was significant improvement in drug homogeneity (CV was only approximately 4%). Following mixing for longer time (15 minutes) there was significant decrease in the magnitude of the mean specific charge. Longer mixing results in no improvement in drug homogeneity and content uniformity with no significant change in the electrostatic chargeability.

Figure. 5.15. (Prosolv90M + CM), unlike the previous example of Prosolv50M, for Prosolv90M there was significant decrease in the magnitude of electrostatic charges following mixing for 5 minutes to reach an optimum level after 15 minutes of mixing, to increase significantly after longer mixing. The best content uniformity with minimum mean specific charge for both Prosolv90M and lab mix 90M where achieved after mixing time of 15 minute.

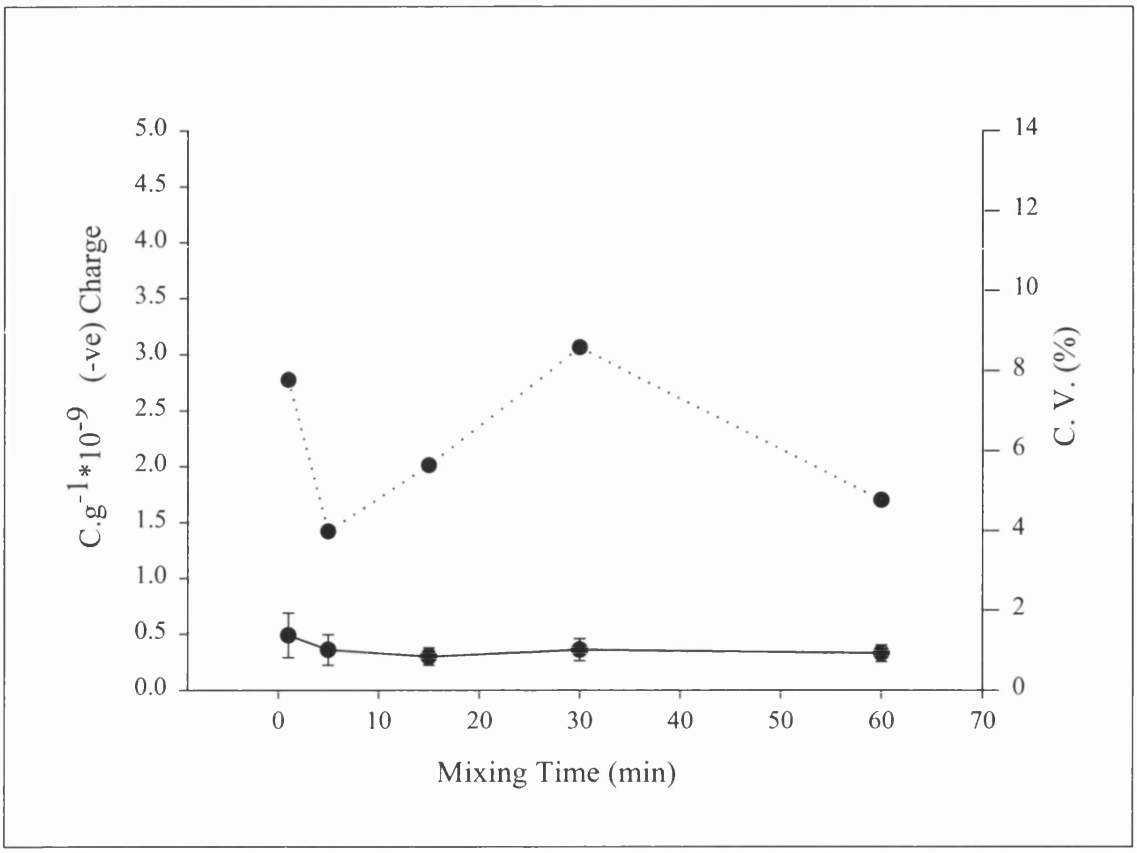



**Fig. 5.11.** Correlation between mixing time, CV and mean specific charge for lab mix 50M following flow of the powder mix on a treated plastic chute (_____) charge and (……..) C.V.

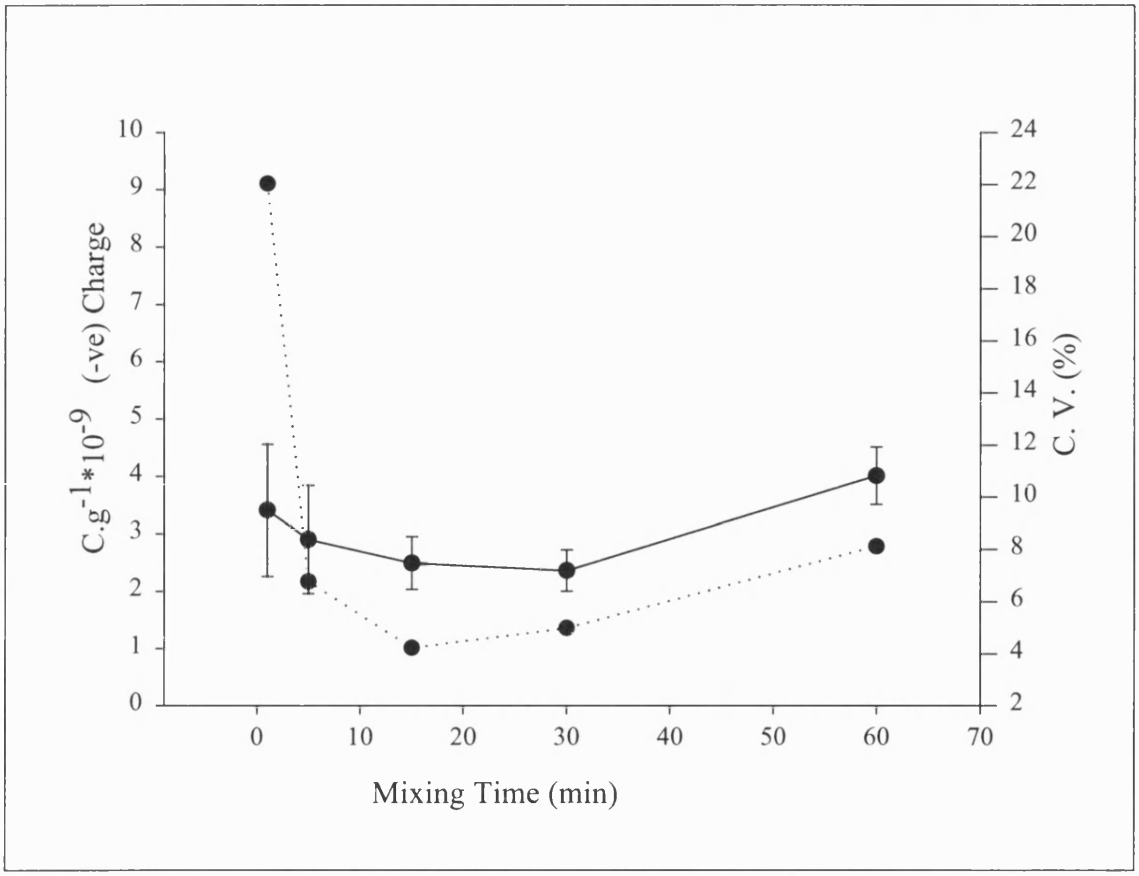



**Fig. 5.12.** Correlation between mixing time, CV and mean specific charge for Prosolv50M following flow of the powder mix on a treated plastic chute (_____) charge and (……..) C.V.

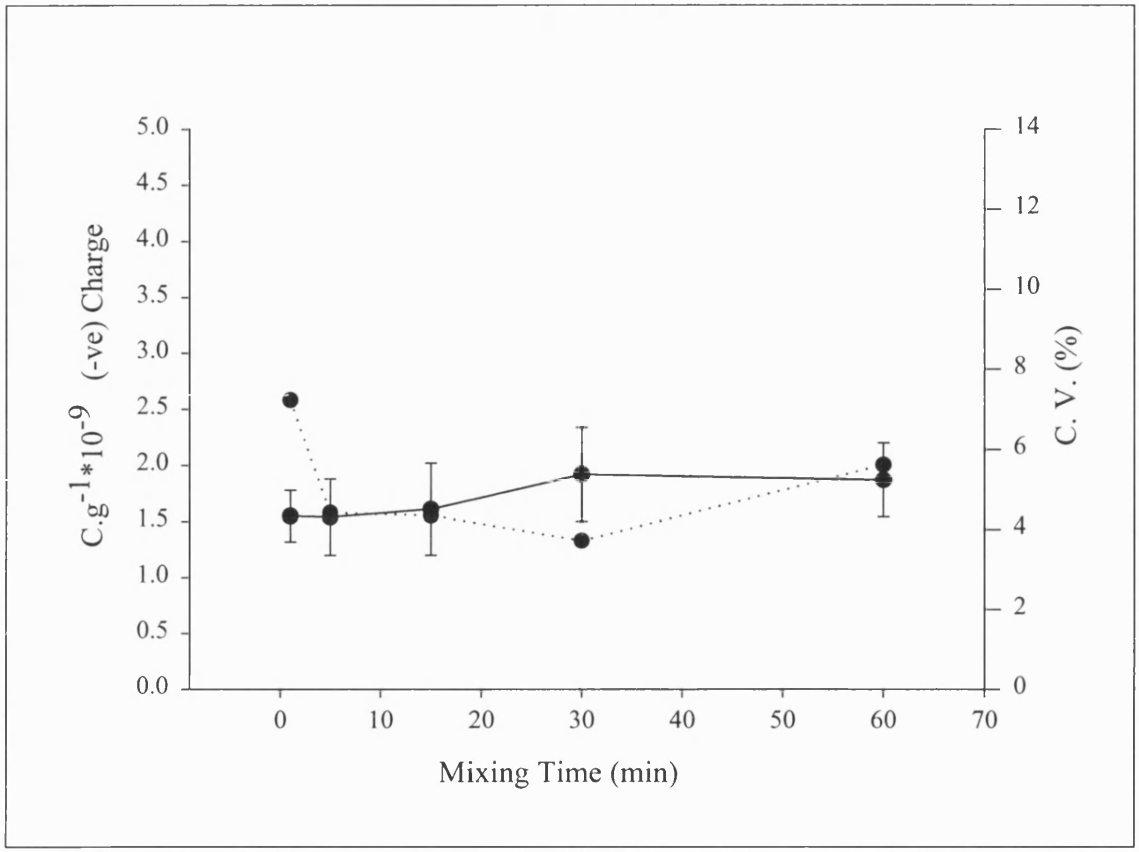



**Fig. 5.13.** Correlation between mixing time, CV and mean specific charge for Emcocel 90M following flow of the powder mix on a treated plastic chute (_____) charge and (……..) C.V.

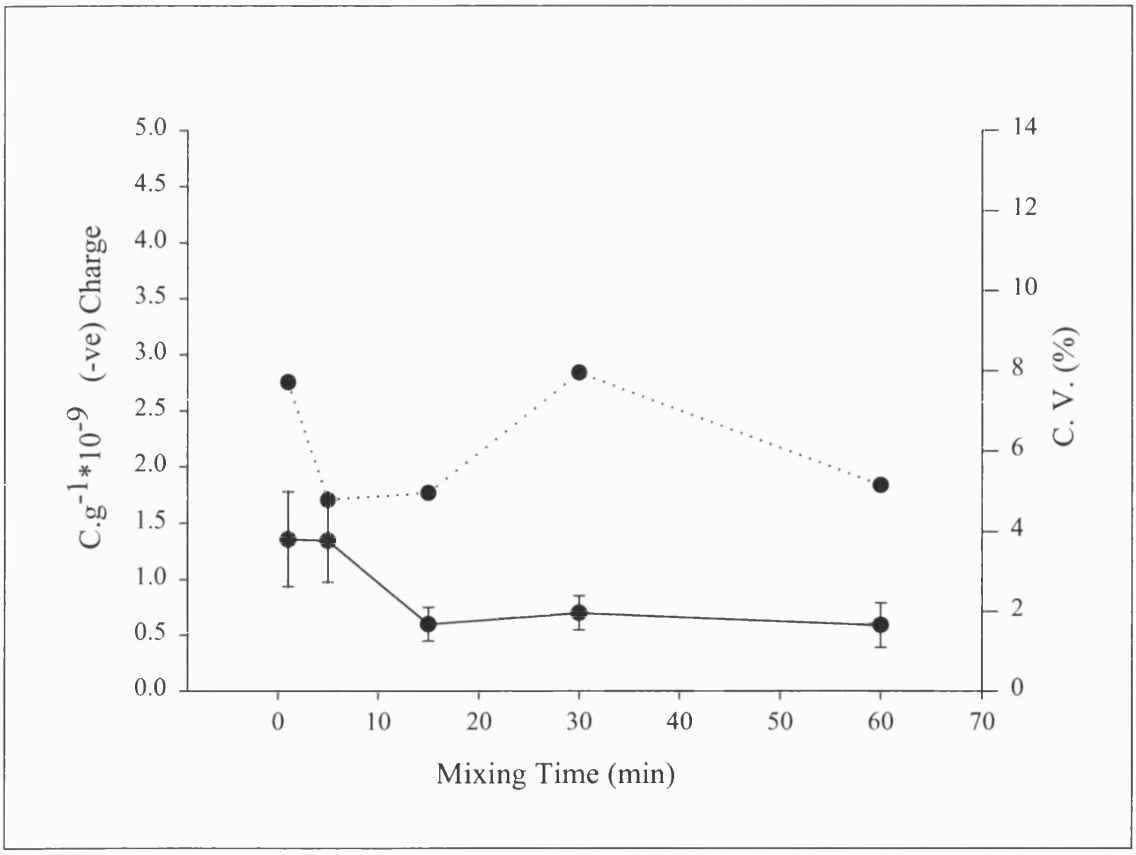



**Fig. 5.14** Correlation between mixing time and CV and mean specific charge for lab mix 90M following flow of the powder mix on a treated plastic chute (_____) charge and (.....) C.V.

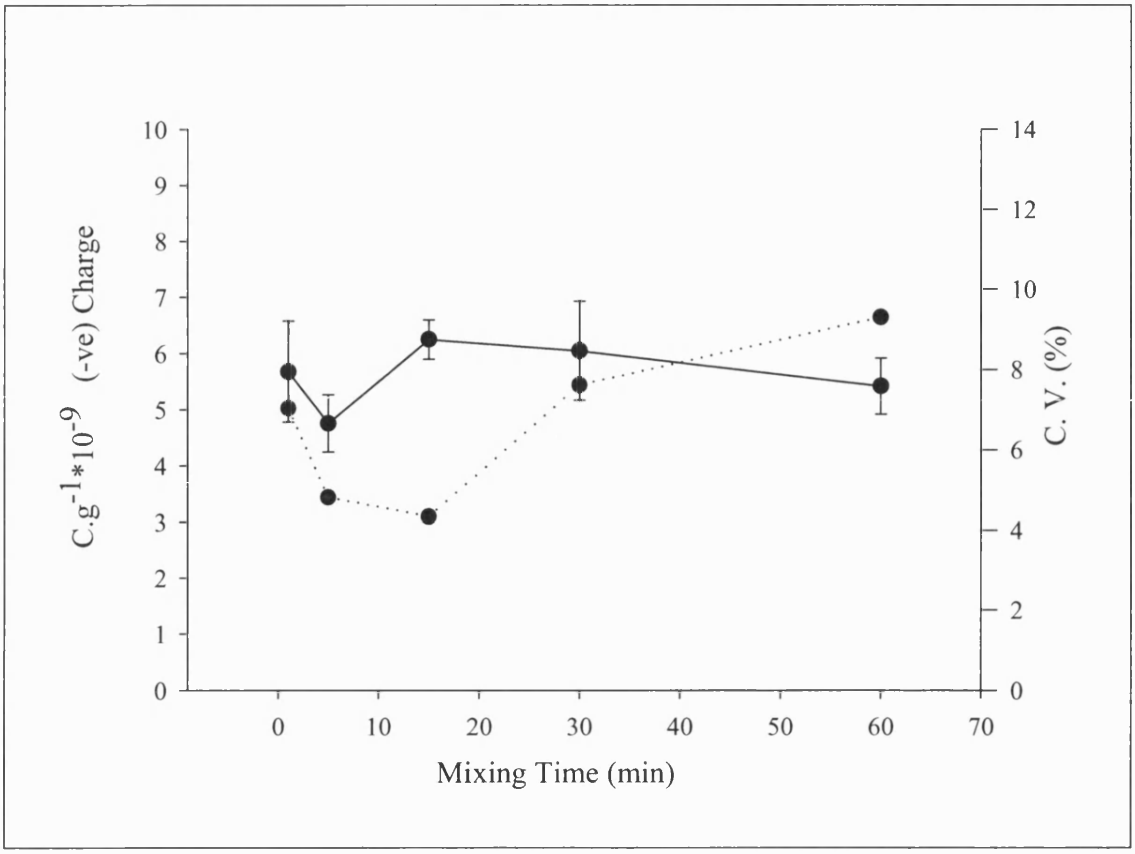



**Fig. 5.15** Correlation between mixing time and CV and mean specific charge for Prosolv90M following flow of the powder mix on a treated plastic chute (_____) charge and (……..) C.V.

*5.3.8.2. Effect of magnesium stearate (MS) on mean specific charge for pharmaceutical powder mixes*

Figures 5.16-5.18 show the mean specific charge (MSC) profiles for Emcocel 50M, lab mix 50M and Prosolv50M with chlorpheniramine maleate before and after addition of MS.

Generally, MS has increased the (MSC) for all blends investigated. For Emcocel 50M figure 5.16 MS has increased the charge at the right beginning of the mixing (1minute) after which significant decrease has occurred. There is no significant difference after 5 minute mixing between the charge of this blend before and after the addition of MS. The effect of MS on the overall electrostatic charge properties of the ternary systems (EM50/CM/MS) is very interesting. While MS alone acquired electropositive charges following flow on treated plastic and metal chute surfaces, yet the effect on the electrostatic charges of the binary mix of EM50/CM was a significant increase in the e electronegative charges of the binary system after 1minute mixing. However, after longer mixing (5 to 30 minutes) there was a significant decrease in electronegative charges acquire by the binary mix. Initially and during first minute of mixing the lubricant exists in an agglomerated form, but after longer mixing and due to the shear forces the lubricant film becomes more evident and complete which results in the significant decrease in electro-negativity described earlier.

Figure 5.17 (lab mix 50M) as it seen, mixing time has significant effect on the (MSC) for ternary and quaternary mixes after the addition of MS. However, there is approximately five fold increase in the specific charge as a result of adding MS.

Figure 5.18 (Prosolv50M), in comparison to ternary and quaternary blends of lab mix 50M (figure 5.17), level of charge had increased when Prosolv50M was used in the mix. In contrast to the five folds increase in the (MSC) due to the addition of MS in the lab mix 50M, Prosolv50M has resisted the effect of MS on the level of charge. The addition of MS has resulted only in 1.5 fold increase at mixing period between 5-30 min. Also, as in the case of lab mix 50M, in the presence of MS in the ternary blend of Prosolv50M increased the (MSC). For the binary mix, initial mixing time for 1 minute decreased the charge followed by sharp increase at longer mixing time (60 min). While in the case of ternary mixes, initially (MSC) increased then followed by gradual decrease after 5 minute mixing.

Figures 5.19-5.21 show the mean specific charge profiles for Emcocel 90M, lab mix 90M and Prosolv90M with chlorpheniramine maleate before and after addition of MS.

Figure 5.19 (Emcocel 90M) in comparison to the (MSC) profile for Emcocel 50M (figure 5.16), MS in Emcocel 90M increased the level of charge at mixing period between 1 minute and 15 minute. After 15 minute MS had no significant effect on the (MSC) in ternary mixes.

For both Emcocel 50M and 90M (fig. 5.16 and 5.19), mixing time has no effect on the chargeability for binary mixes while it has an obvious effect when MS is added.

In figure 5.20 (lab mix 90M), MS has no obvious effect on the (MSC) in comparison to the large effect that it has on the lab mix 50M and on the Emcocel 90M at the initial mixing period. This means that lab mix 90M has certain level of resistance to the effect of MS and also to the mixing time.

Similarly, Prosolv90M (figure 5.21) has shown resistance to the effect of MS at mixing period between 1-15 minute after which charge has decreased. Yet, in comparison to the lab mix 90M (figure 5.20) there has been increase in the level of the charges for Prosolv90M before and after addition of the MS. At early mixing there isn't much difference in the (MSC) between binary and ternary mixes and also mixing time has no significant effect on the (MSC) for binary mixes.

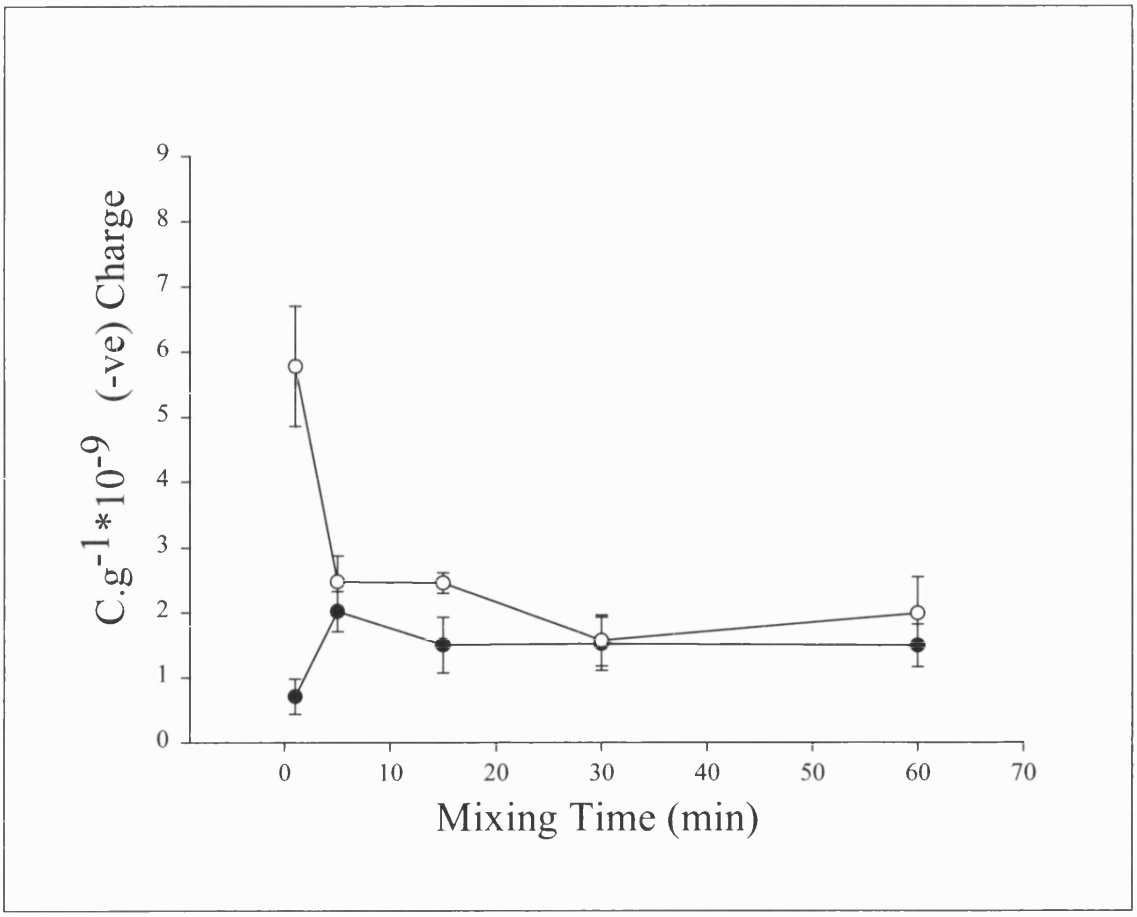



**Figure 5.16.** Effect of magnesium stearate (MS) on electrostatic charge of pharmaceutical powder mixes containing Emcocel 50M and (CM) (●) and Emcocel 50M, (CM) and MS (○) following flow on treated plastic chute.

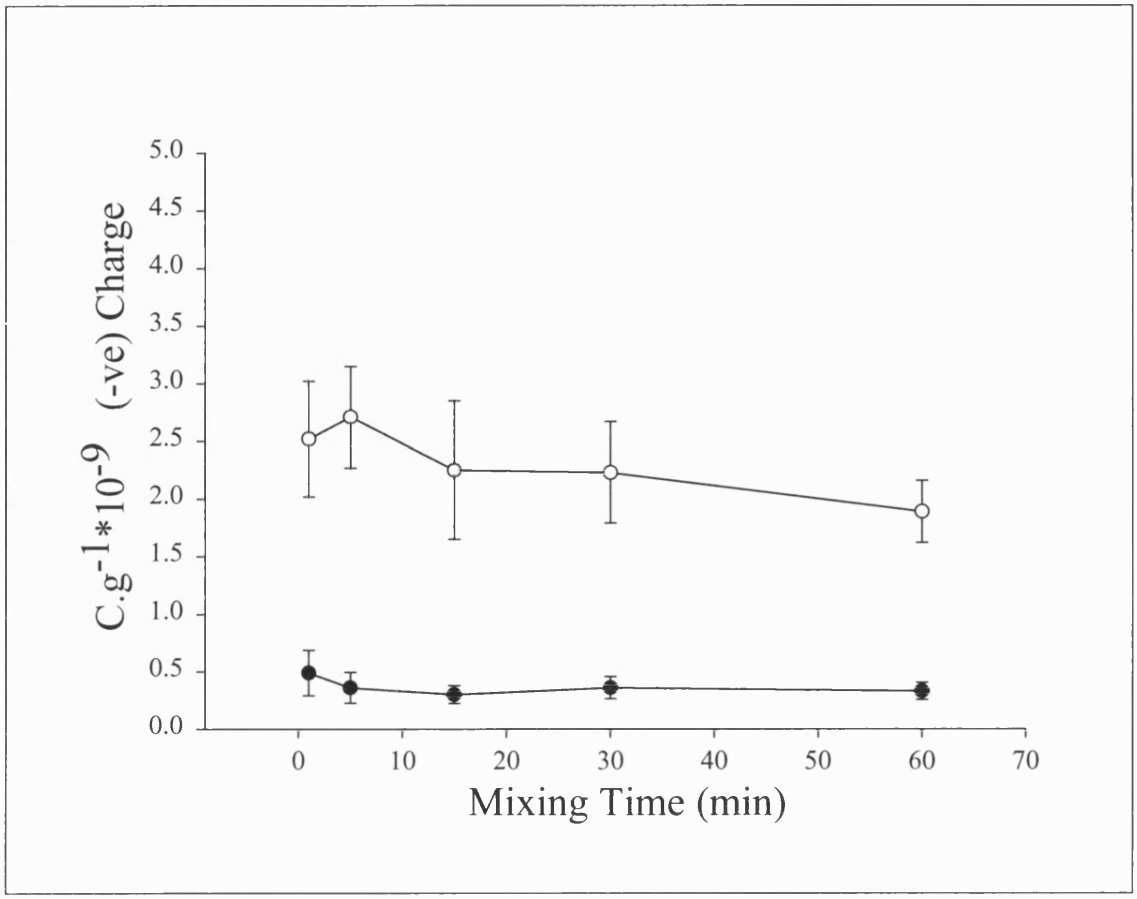



**Figure 5.17.** Effect of magnesium stearate (MS) on electrostatic charge of pharmaceutical powder mixes containing lab mix 50M and (CM) (● and lab mix, (CM) and MS (○ following flow on treated plastic chute.

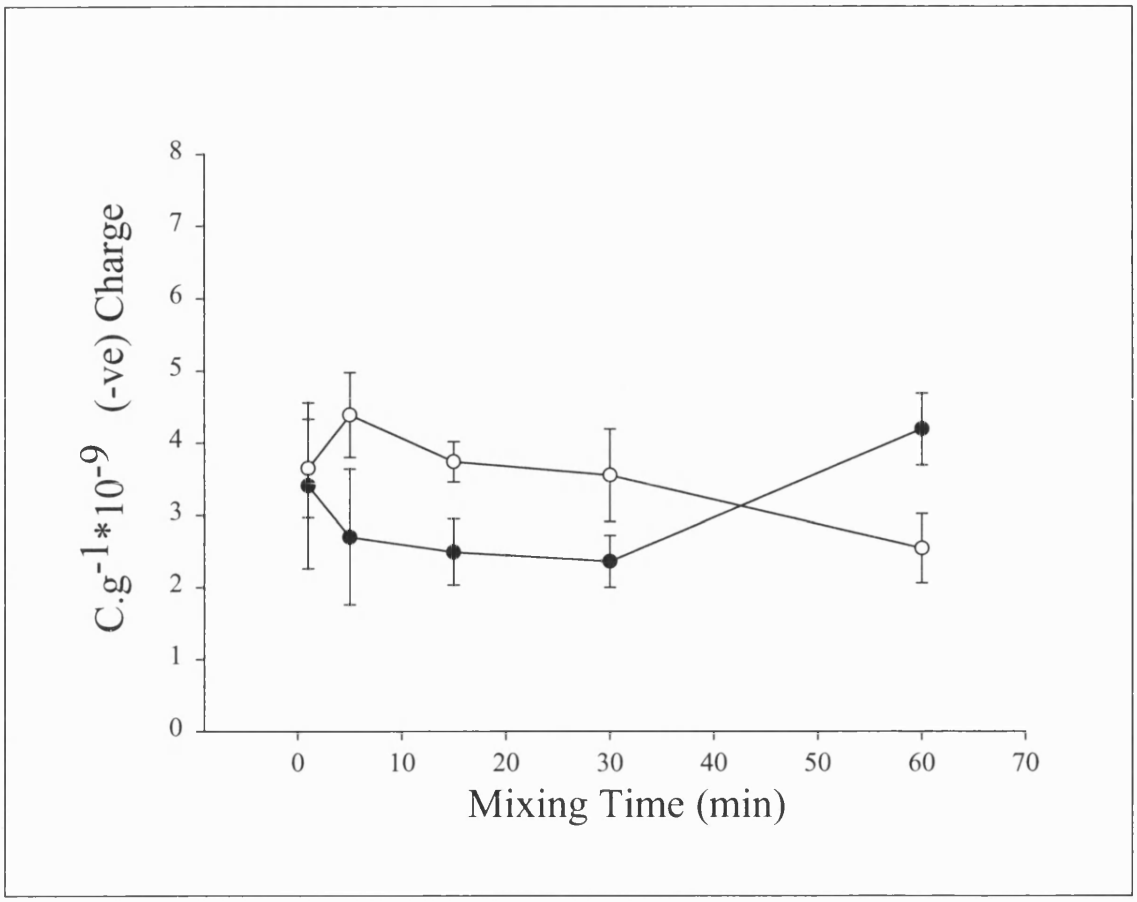



**Figure 5.18.** Effect of magnesium stearate (MS) on electrostatic charge of pharmaceutical powder mixes containing Prosolv50M and (CM) (◕ and Prosolv50M, (CM) and MS (◔ following flow on treated plastic chute.

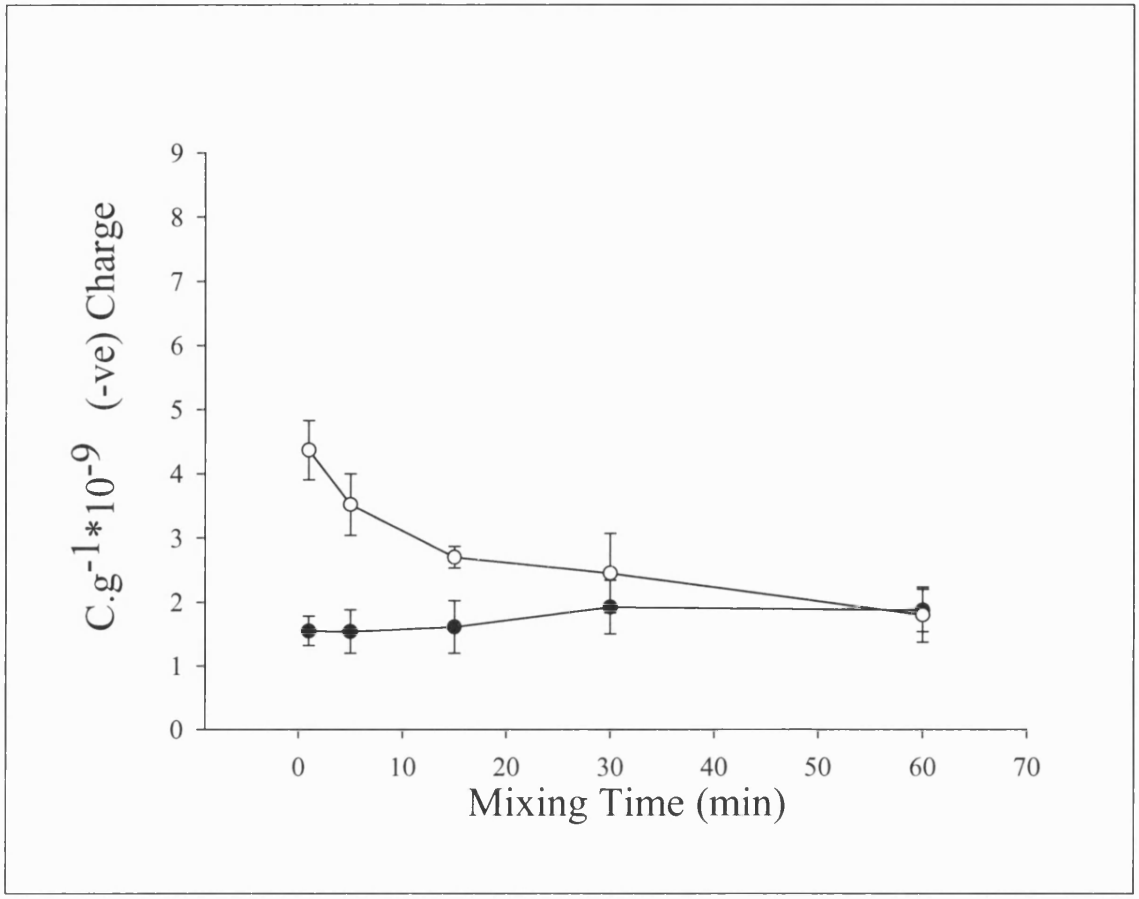



**Figure 5.19.** Effect of magnesium stearate (MS) on electrostatic charge of pharmaceutical powder mixes containing Emcocel 90M and (CM) (●, Emcocel 90M, (CM) and MS (○) following flow on treated plastic chute.

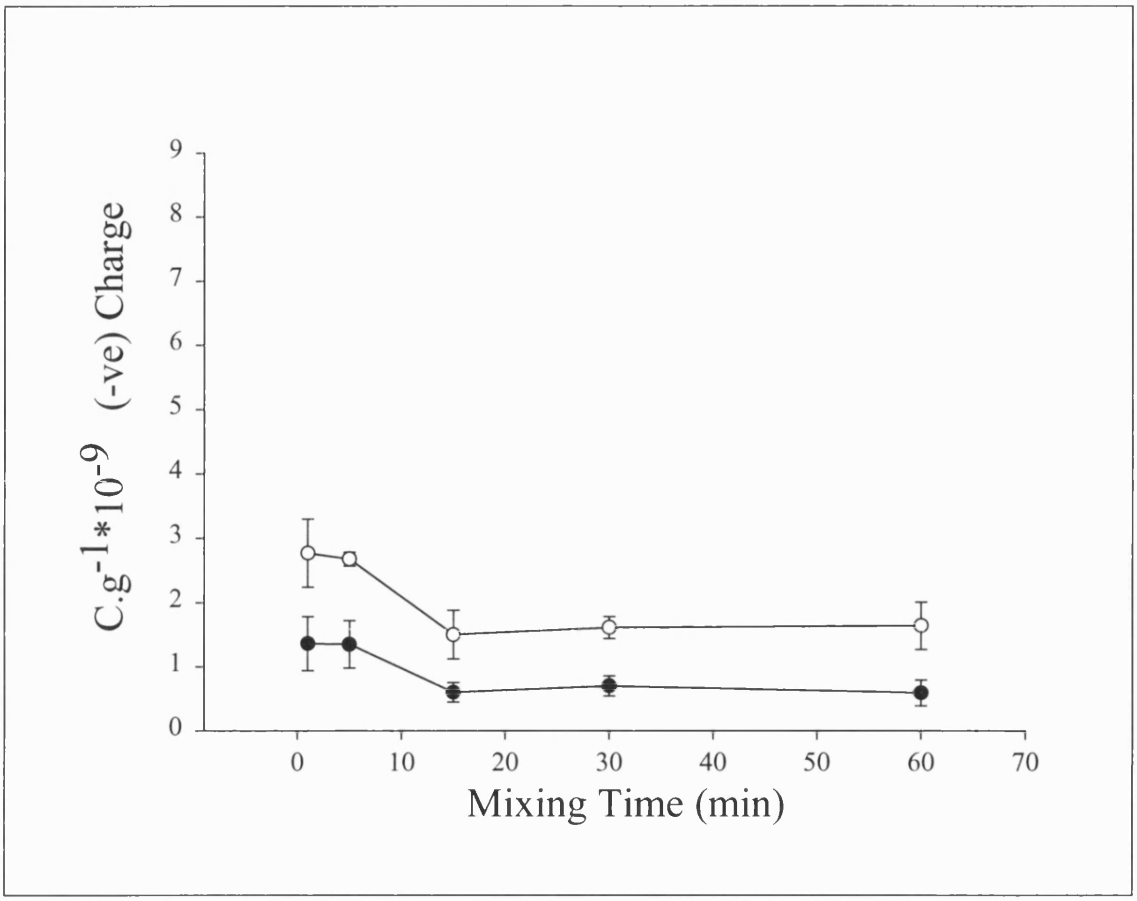



**Figure 5.20.** Effect of magnesium stearate (MS) on electrostatic charge of pharmaceutical powder mixes containing lab mix 90M and (CM) (●), lab mix 90M, (CM) and MS (○) following flow on treated plastic chute.

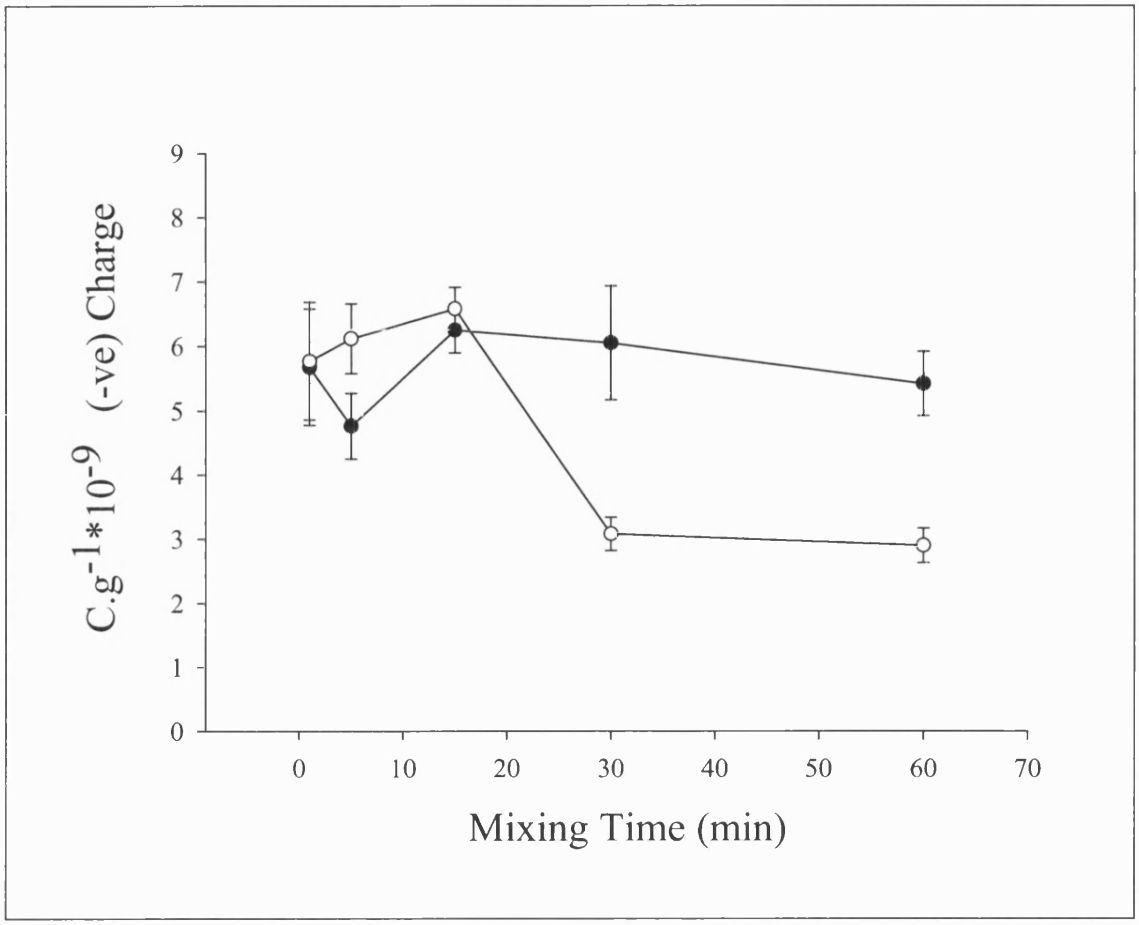



**Figure 5.21.** Effect of magnesium stearate (MS) on electrostatic charge of pharmaceutical powder mixes containing Prosolv90M and (CM) (●, Prosolv90M, (CM) and MS (○ following flow on treated plastic chute.

**Table 5.11** Effect of mixing time (min) on the mean specific charges ($C.g^{-1}X10^{-9}$) CV% of different powder mixes after adding magnesium stearate 1% investigated following flow on a metal chute.

| Mixing time (minutes) | 1 | | 5 | | 15 | | 30 | | 60 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sample | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Emcocel 50M | 1.08 | 22.97 | 0.96 | 16.01 | 1.15 | 17.54 | 0.53 | 29.24 | 0.64 | 25.96 |
| Emcocel 90M | 2.67 | 35.95 | 0.86 | 24.91 | 1.90 | 29.59 | 0.36 | 29.40 | 0.88 | 22.92 |
| Prosolv50M | 2.21 | 24.44 | 1.74 | 27.40 | 1.02 | 28.45 | 1.00 | 19.98 | 0.66 | 29.43 |
| Prosolv90M | 2.74 | 27.00 | 2.74 | 15.90 | 2.07 | 12.18 | 1.36 | 28.31 | 1.02 | 23.62 |
| Lab mix 50M | 3.38 | 11.19 | 4.90 | 8.96 | 4.46 | 10.71 | 4.87 | 8.05 | 3.92 | 12.50 |
| Lab mix 90M | 0.41 | 32.69 | 0.45 | 26.87 | 1.04 | 18.98 | 0.41 | 22.11 | 1.12 | 24.97 |
| Emcompress | 0.46 | 39.49 | 0.41 | 30.06 | 0.31 | 18.56 | 0.41 | 23.60 | 0.65 | 26.94 |
| LactoseD30 | 1.90 | 21.25 | 1.63 | 10.92 | 1.89 | 14.20 | 1.87 | 18.95 | 2.20 | 9.26 |

**Table 5.12** Effect of mixing time (min) on the mean specific charges ($C.g^{-1}X10^{-9}$) CV% of different powder mixes after adding magnesium stearate (1%) investigated following flow on a plastic chute.

| Mixing time (minutes) | 1 | | 5 | | 15 | | 30 | | 60 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sample | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Emcocel 50M | 2.05 | 22.97 | 1.29 | 16.01 | 2.22 | 17.54 | 2.75 | 29.24 | 2.82 | 25.96 |
| Emcocel 90M | 0.79 | 35.95 | 1.50 | 24.91 | 3.19 | 29.59 | 2.75 | 29.40 | 1.82 | 22.92 |
| Prosolv50M | 2.60 | 24.44 | 1.66 | 27.40 | 1.16 | 28.45 | 0.52 | 19.98 | 1.45 | 29.43 |
| Prosolv90M | 2.69 | 27.00 | 1.72 | 15.90 | 0.79 | 12.18 | 2.03 | 28.31 | 3.27 | 23.62 |
| Lab mix 50M | 2.47 | 11.19 | 3.22 | 8.96 | 3.36 | 10.71 | 3.28 | 8.05 | 3.06 | 12.50 |
| Lab mix 90M | 4.97 | 32.68 | 3.66 | 26.87 | 2.97 | 18.98 | 3.58 | 22.11 | 3.06 | 24.97 |
| Emcompress | 1.74 | 39.49 | 2.47 | 30.06 | 1.69 | 18.56 | 1.50 | 23.66 | 1.06 | 26.94 |
| Lactose D30 | 3.41 | 21.25 | 5.27 | 10.92 | 5.02 | 14.20 | 4.81 | 18.95 | 5.62 | 9.24 |

**Table 5.13.** Effect of mixing time (min) on the mean specific charges ($C.g^{-1}X10^{-9}$) CV% of different powder mixes after adding magnesium stearate (1%) investigated following flow on a treated plastic chute.

| Mixing time (minutes) | 1 | | 5 | | 15 | | 30 | | 60 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sample | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Emcocel 50M | 5.78 | 16.61 | 2.48 | 16.16 | 2.46 | 19.41 | 1.57 | 24.85 | 1.99 | 28.25 |
| Emcocel 90M | 4.37 | 29.01 | 3.52 | 33.76 | 2.70 | 32.06 | 2.45 | 25.58 | 1.80 | 28.09 |
| Prosolv50M | 3.65 | 18.85 | 4.39 | 13.55 | 3.74 | 7.57 | 3.55 | 18.16 | 2.54 | 18.99 |
| Prosolv90M | 5.77 | 15.88 | 6.12 | 8.82 | 6.58 | 5.02 | 3.08 | 8.52 | 2.90 | 11.11 |
| Lab mix 50M | 2.52 | 20.03 | 2.71 | 16.48 | 2.25 | 27.02 | 2.23 | 20.07 | 1.89 | 14.52 |
| Lab mix 90M | 1.90 | 28.39 | 1.88 | 32.18 | 1.32 | 29.44 | 1.59 | 11.22 | 1.72 | 21.48 |
| Emcompress | 2.77 | 35.62 | 2.43 | 22.56 | 2.21 | 25.07 | 2.84 | 24.15 | 2.76 | 24.05 |
| LactoseD30 | 3.68 | 25.75 | 6.02 | 23.58 | 8.44 | 22.40 | 7.18 | 20.20 | 10.62 | 14.77 |

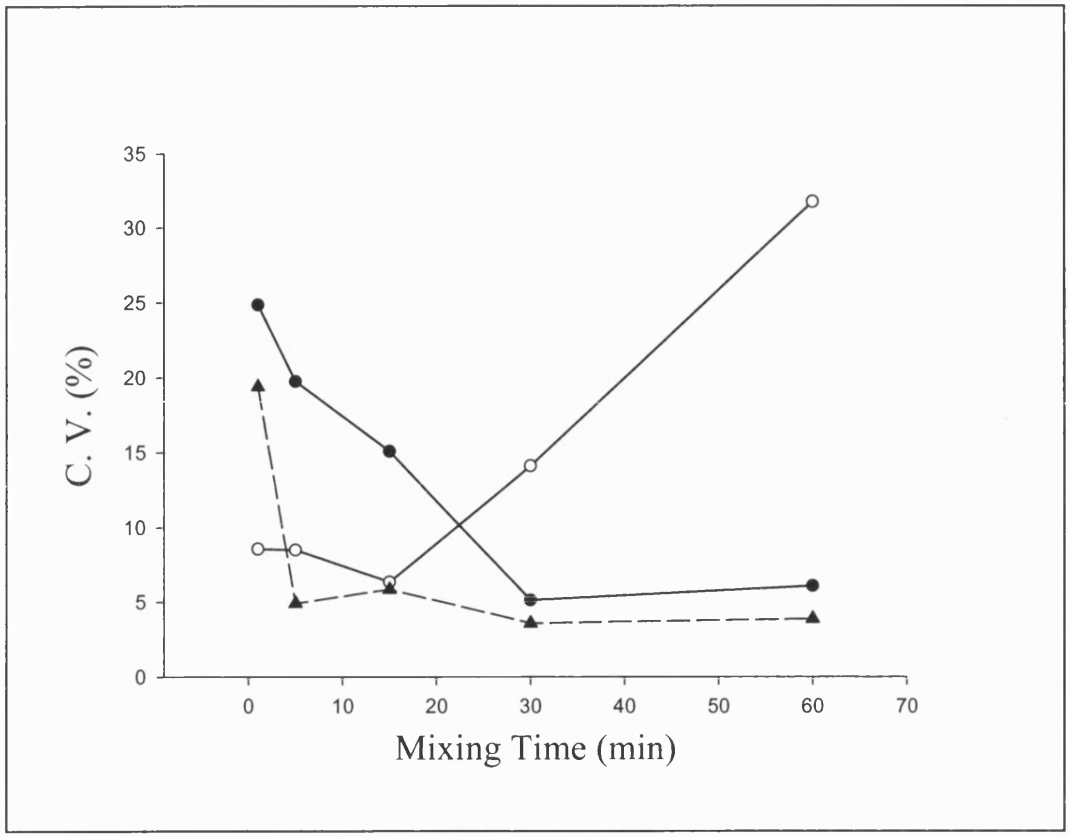



**Figure 5.22**. Effect of mixing time on drug homogeneity for Emcocel 50M (●, lab mix 50M (○) and Prosolv50M (▲)

Figure 5.22. summarises the effect of mixing time on drug homogeneity for the different powder mixes investigated following the addition of MS. As discussed earlier Prosolv50M containing system was not affected by the addition of magnesium stearate while the other two powder systems were significantly affected by the addition of the lubricant. These results suggest that the use of Prosolv50M instead of Emcocel 50M or a lab mix of Emcocel 50M and CS is beneficial in producing homogeneous and stable powder mixes suitable for further development as solid dosage forms (e.g. tablets or capsules).

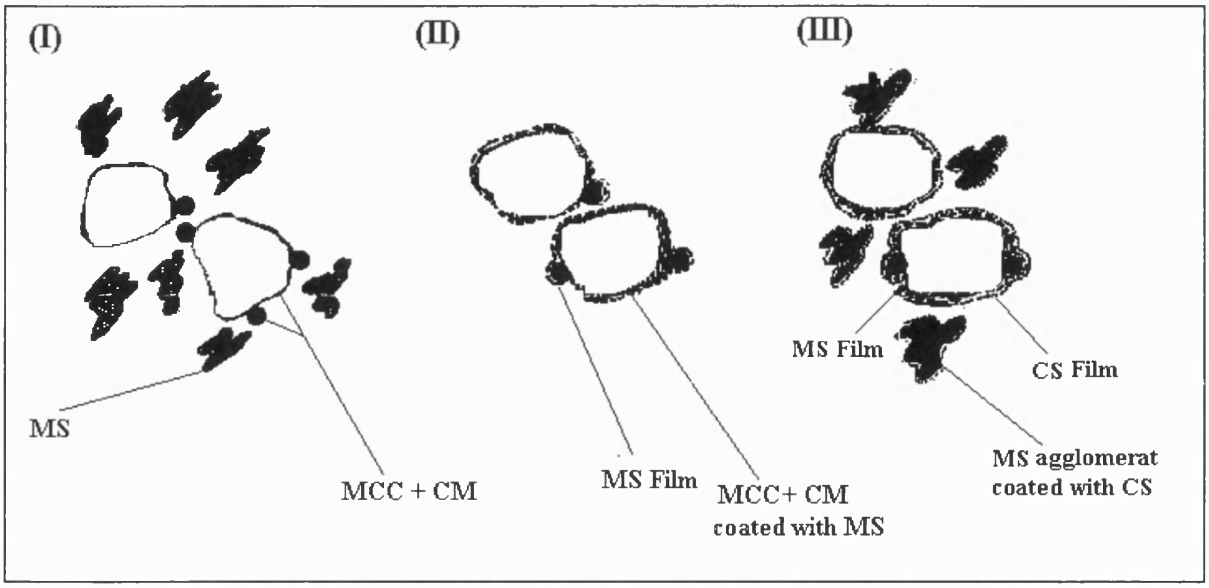



**Fig.5.23** Enrobement of magnesium stearate (MS) with colloidal silica (CS).

(I) Configuration of adhesive units of MCC and chlorpheniramine maleate (CM).

(II) Hydrophobic film formation of MS.

(III) Addition of CS and enrobement of MS.

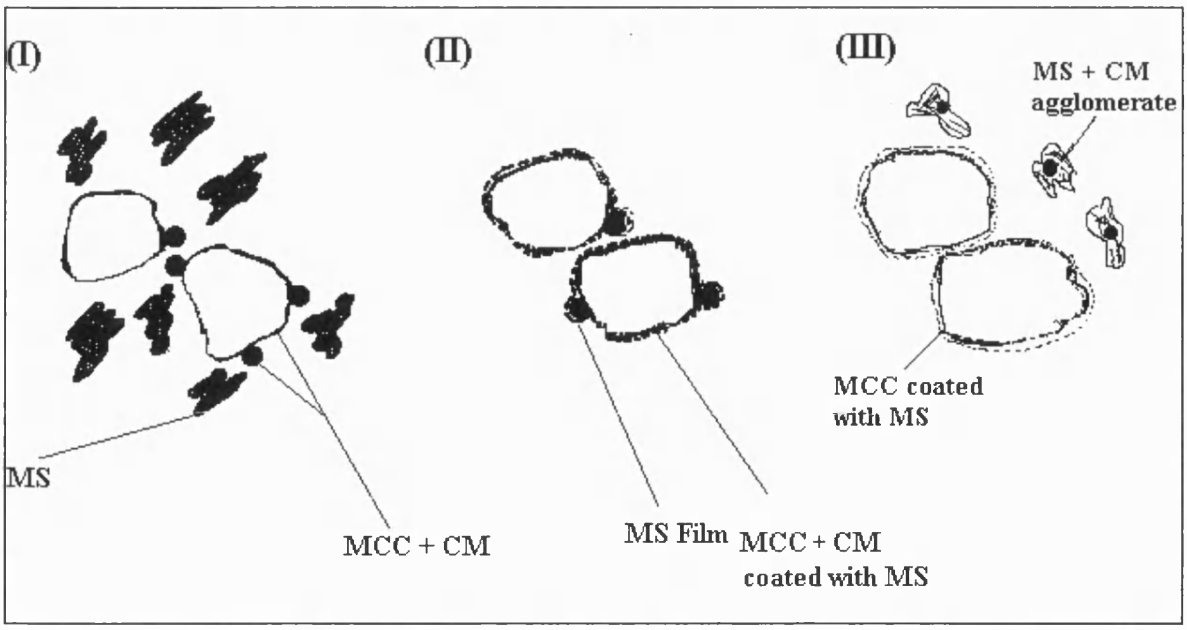



**Fig.5.24.** Stripping effect of magnesium stearate (MS) on chlorpheniramine maleate (CM).

(I) Configuration of adhesive units of MCC and chlorpheniramine maleate (CM).

(II) Deagglomeration of MS and formation of lubricant film.

(III) Stripping of (CM) by MS.

### *5.4 Discussion*

It can be seen that the mixing properties of the various MCC materials differ significantly. The properties of the Prosolv systems seem particularly advantageous. Although the beneficial properties in terms of mixing show some correlation with the flow results previously described no causative effect can be demonstrated at this time. Once again the electrostatic results proved inconclusive. Nevertheless the effect is real and measurable and suggests that Prosolv materials may have some further benefits (in addition to improved compressibility and flow) in direct compression processing compared to conventional materials.

Of particular note is the stabilisation effect with regard to magnesium stearate. This material is frequently added at the end of the processing cycle, directly before tableting. This is because it weakens tablets (and in the case of dry blends) destabilises blends. The additional processing steps and their sensitive nature makes this a particularly problematic step in processing.

It has already been demonstrated that Prosolv is particularly resistant to the deleterious tablet weakening effects of magnesium stearate (Sherwood and Becker, 1998). The fact that Prosolv blends resist destabilisation by magnesium stearate regardless of order of addition, in contrast to that found by Ahmed, may also be a useful property. This would seem, at this time, to be a unique benefit of Prosolv.

This certainly allows more latitude in manufacture of blends and should aid the scalability of systems for manufacture. In the future it may allow the removal of the

additional step in manufacture that is required when magnesium stearate is used. However it is recognised that this sort of mixing may have other disadvantageous effects (e.g. coating the drug with insoluble magnesium stearate may lengthen dissolution times).

# Chapter 6

## *6.1. General Discussion*

The project aimed to discover whether the Aero-Flow apparatus could be a useful apparatus in determining the flow of pharmaceutically relevant materials. The instrument proved itself to be capable of producing reproducible results, *under controlled conditions.* It would seem clear that careful storage and manipulation of the powders and careful handling of the equipment is necessary. Parameters which need close attention are the volume of powder added, the humidity at which it is stored, the representative nature of the sample and the static control within the drum. A feature of the Aero-Flow which might be regarded as problematic (and unavoidable) is that small particle size (poor flowability) powders may appear to give good flow due to a spheronisation or balling effect, this has to be monitored to reduce the possibility of artefacts being produced.

In the future it would be useful to discover whether additional information (as well as the mean and variance of the flow) can give useful data. The availability of now of hardware capable of running at different rates may provide additional useful data. In addition the use of the available fractal data might be beneficial, particularly if it is timesliced to discover whether there are any changes in the powder during the testing process. A couple of changes in the hardware may also be helpful. The use of a metal or metal coated drum (this may not be able to use light as the measuring source) would be a useful development.

The Aero-Flow instrument did not give good correlation with other flow apparatus tested nor with the tablet weight variation test. This is often a feature of new flow

methodologies, and is perhaps to be expected. All completely novel methods measure slightly (or substantially) different properties of a powder. It is important under these circumstances that the powder scientist or formulator chooses the parameter which is most relevant to the situation under examination. The poor correlation with the tablet apparatus may be due to the different materials (metal vs. Perspex) of construction of the apparatus but there may be other differences. It may be that the relatively slow speed of the tablet machine used compared with a production speed did provide a sufficient test to the powder. This is indicated by the relatively low RSD of the tablet weights, even for relatively poor flowing powders. Under more testing conditions (e.g. a high speed tablet press) there may be better correlation. An extensive study with different rates of speed in the drum and tablet machines would be beneficial.

The Aero-Flow apparatus demonstrated, unequivocally, that under the conditions tested Prosolv materials gave significantly improved flow. This has been seen in other situations and may be expected. However this work further showed that the silicification process produces a material which resists the effect of humidity to a much greater extent than conventional materials. This may have some benefits in some manufacturing situations.

It is interesting that different methods of adding silica have differing effects on flow properties. It has previously been demonstrated that silica added in the normal way are *less* beneficial in improving tablet strength, and may even prove detrimental to tablet strength. It would appear that, in terms of improving flow, conventional methods of addition are best, and that 'ball-bearings' of silica are of greater benefit than a well dispersed particulate layer, in improving overall flow and reducing sensitivity to moisture. Additional experiments would be necessary whether *degrees* of dispersion of silica could

produce a graded effect, i.e. does silica dry mixed and added with considerable shear produce intermediate results or benefits.

Electrostatics proved difficult and frustrating to measure and quantify. This is, perhaps, to be expected. Despite considerable efforts to reduce these problems only limited insights could be gained. Some validation may be seen from the fact that charge clearly diminished as the relative humidity of storage of the powders increased. There was some indication that Prosolv materials were more efficient at dispersing charge across their surface. This may explain the beneficial flow results seen and initially formed the basis of seeing whether the Prosolv could form more stable blends. However in retrospect the results would have to be carried out under considerably more controlled conditions (control particle size, reproducible sample, humidity and tempreture) in order to get reproducible, valid results. Some benefit may be gained from measuring the direct output from the electrometer (perhaps on a chart recorder) so that the overall area under the curve is measured rather than a simple peak effect. However, as others have seen there are considerable advances to be made in electrostatic characterizations.

The mixing work carried out once again provided some provisional insights into the possible nature of how Prosolv may perform under blending conditions. There is some data here which indicate that blends come to equilibrium more quickly with Prosolv, although this would have to be investigated thoroughly. The relative stability of the blends was not measured using, for instance, a centrifuge technique. This technique can measure, when used correctly, the adhesion forces of particles to substrates, and may have provided useful information in this study. Recent developments on the Atomic Force Microscope (AFM), which can measure the same interactions on an individual particle basis, could also

have provided some data. If Prosolv blends are more or less stable than their conventional equivalents it should be quantified and the implications discovered.

Clearly considerable further experiments would have to be done to discover whether this benefit extends to other situations. Different drugs, blend ratios and other parameters would have to be looked at in detail. The use of micronised material would allow the discovery of whether adhesional forces are improved with the novel materials, in ordered mixes. Further examination of completely different systems, where drug and excipient are in the same size range would allow the discovery of whether the improved flow of silicified powders in a mixer may aid randomization and distribution in blends where adhesive forces do not predominate (i.e. the blend is non-interactive). Preliminary analysis of a system containing potassium chloride as a model drug did not prove conclusive in this regard.

The beneficial effects of Prosolv materials in resisting the effects of magnesium stearate is a novel and potentially valuable discovery. These benefits extend beyond the results previously seen whereby colloidal silica was only beneficial in certain situations (e.g. in the correct mixing order). The explanation of this benefit would only be seen after many further experiments, and would then have to be demonstrated in some, or all, of the situations outlined above. It would further be interesting to know whether these benefits extended to different mixing vessels and situations.

Once again the electrostatic results may provide some initial insights into the processing going on within the blend. Magnesium stearate may destabilize blends by putting in additional charges into the system (which attract the drug particles to the stearate

rather than the stabilizing carriers). There were some indications that Prosolv could disperse this charge increase more efficiently than other materials (including dry mixes of MCC and colloidal silica) but the caveats from above also apply.

Although it is known that there is an attraction between colloidal silica and magnesium stearate it is not yet clear how the magnesium stearate is distributed in these blends, in the conventional and novel situation. This could be quantified, perhaps using SEM techniques combined with X-ray microanalysis.

## *6.2. Future Work:*

In this study colloidal silica was found to improve powder flow. Among at the three concentrations of colloidal silica tested (1%, 1.7% and 2%) the best flow was observed in presence of 2% w/w colloidal silica. Yet, the effect of high concentration of $SiO_2$ e.g. 6% on the flowability needs to be investigated.

The problem after tablet formula has been carefully developed, is scale –up from development to pilot to commercial production. There is no set formulas for scaling up as each particulate system, dry or wet, has its own particle-particle interactions. Moreover, there has been very little mixing data accumulated to provide a solid data base for a mathematical scale-up model. For scaling up procedure mixes selection, time and speed of mixing and ratios of active ingredient to tablet weight need to be optimised in order to achieve better homogeneity and less electrostatic charge.

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